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Original Communications

THE TONIC NECK REFLEX IN THE HUMAN INFANT

MORPHOGENETIC AND CLINICAL SIGNIFICANCE

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THE tonic neck reflex is an asymmetric pattern of behavior, common to man and beast. Magnus, in his classic work on *Körperstellung*, reported an analysis of the postural reaction of decerebrate quadrupeds when their heads were experimentally turned to an extreme right or left position. He found a characteristic response: (a) extension of the forelimb on the side toward which the head was turned; (b) flexion of the opposite forelimb. The reflex occurred in pure form when the labyrinths were extirpated, and it was ascribed to proprioceptive impulses arising in the neck from torsion.

Magnus demonstrated the existence of the tonic neck reflex in idiots and patients suffering from extrapyramidal tract lesions; he was unable to induce the reflex in some twenty-six normal infants from a few hours to 16 weeks of age. He came to the conclusion that in man the tonic neck reflex is a pathologic phenomenon.[1]

This conclusion is somewhat amazing because we have found the tonic neck response a ubiquitous, indeed, a dominating characteristic of normal infancy in the first 3 months of life. In a clinical sense the response should be regarded as abnormal only when it occurs in children of more advanced age who are suffering from arrest or damage of the central nervous system.

The accompanying illustrations show that this attitudinal pattern is clearly evident in the spontaneous waking postures of the normal infant, whether he lies quiescent or active. We shall use the convenient symbol T.N.R. to designate the general pattern, both in its quiescent and activated forms.

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Fig. 1 illustrates T.N.R. in a rabbit and in a normal infant. The rabbit is adapted from Magnus; the infant is a healthy 8-week-old subject basking in the photographic dome of our clinic at Yale. Both are in the right T.N.R. attitude.

Fig. 1.—*A*, Right T.N.R. in rabbit induced by head torsion. (Adapted from Magnus.) *B*, Right T.N.R. in normal human infant (aged 8 weeks), spontaneously assumed.

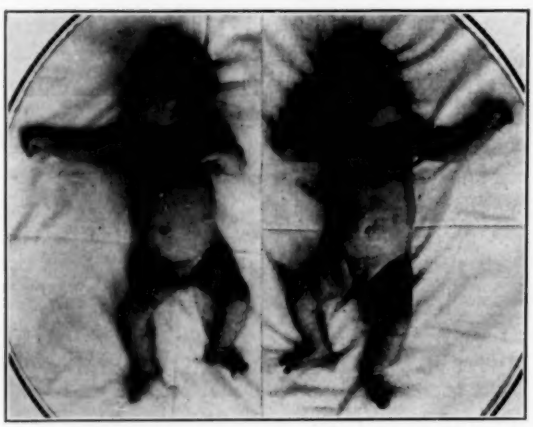

Fig. 2.—*A*, Right T.N.R. in a normal 6-week-old infant. *B*, Left T.N.R. in another normal infant of the same age.

Fig. 2 pictures two normal infants, both 6 weeks of age. One is in right T.N.R., and the other in left T.N.R. In each instance the face-arm and face-leg are in extension, the contralateral extremities in flexion. Note the striking semblance to a fencing stance.

Fig. 3 shows a normal infant who at 1, 6, 8, and 12 weeks of age spontaneously and consistently exhibited a right T.N.R.

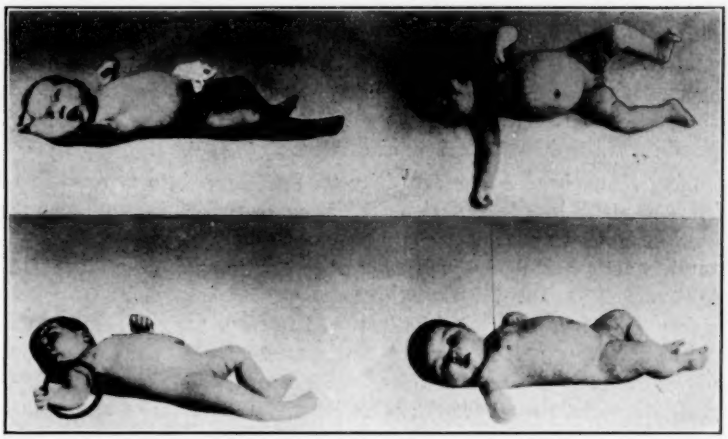

Fig. 3.—Right T.N.R. spontaneously and consistently exhibited in infant V. W. at 1, 6, 8, and 12 weeks of age.

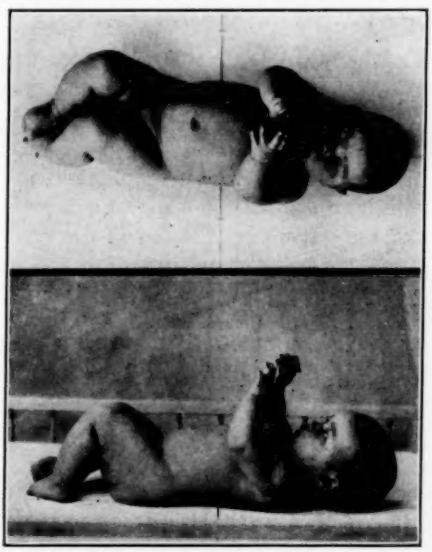

Fig. 4.—Symmetric prehensory and postural patterns in infant V. W., aged 24 weeks. Simultaneous photographs taken with one camera at the zenith and the other at the horizon of the photographic dome.

Fig. 4 pictures the same infant at 24 weeks of age. The spontaneous postural asymmetry of the earlier ages has been superseded by a symmetric attitude in which both arms flex and the hands engage above the chest at the midline. This is a lawful, developmental sequence. The

T.N.R. mechanisms are not extinguished at 24 weeks; they are simply submerged by symmetric, bilateral patterns. In another month the bilateral in turn give way to new unilateral patterns: one-handed reaching, one-handed manipulation and hand-to-hand transfer, and ultimately to well-defined dextrality or sinistrality. Throughout early human development there is an almost periodic, interweaving maturation, now of symmetric and then asymmetric behavior forms, with corresponding shifts in postural manifestations.

During sleep, head and extremities tend to lapse into symmetric or indifferent attitudes of relaxation. Whether drowsing, asleep, or awake the infant's posture may burst into momentary general symmetry, through startle and body jerk reflexes. The prevailing waking attitude, however, during the first three months is characterized by head aversion. The head seeks and holds the mid-position for relatively brief and infrequent intervals. Round heads rotate more freely than long heads in the early weeks, and since head posture initiates arm postures, this difference influences T.N.R. behavior. By 16 weeks of age infants usually show considerable freedom of head movement. I have been able to induce alternating right and left T.N.R. responses in a supine 16 weeks old infant simply by passing an object slowly across the field of vision. This visual stimulus was sufficient to induce a right T.N.R. when my hand moved toward the right, and a left T.N.R. when my hand moved to the left. The infant responded almost like an automaton under photoelectric control. These responses and other manifestations of the tonic neck reflex are delineated in a motion picture film.*[5]

Morphogenetically the human T.N.R. should not be envisaged as a stereotyped reflex but as a growing pattern, changing with the maturity and the economy of the organism. Torsion of the head to one side in a living fetus 20 weeks old arouses a movement of the arm on that side. This is a rudimentary T.N.R. which becomes better defined and elaborated in the latter half of the prenatal period. Fifteen minutes after the birth of a normal infant, I recently detected a greater tonicity in the right as opposed to the left arm (the legs were in equal relaxation). This discrepancy was predictive of a left T.N.R. in which the right, or occiput arm tends to show the greater tonus. The infant was kept under continuous observation for fourteen days and nights, and although he was placed in varying postures, he consistently displayed a waxing left T.N.R. Another infant, belonging to the right wing, was photographed daily in a standard supine position, from the fifteenth day

*This film is based on normative, experimental, and clinical cinema records as follows: (1) Reactions of a supine infant (age 20 weeks) to a dangling ring. Shows symmetry of postural and prehensory approach. (2) Overhead view of infant M. H., consistently showing right T.N.R. at 64, 65, 66, 67, 68 days of age, based on daily cinema records under experimentally repeated conditions. (3) Microphotographic section of a birth lesion of the basal ganglia (status marmoratus). (4) Active T.N.R. of boy A. C., aged 7 years, associated with a basal brain lesion. (5) Active T.N.R. of normal infant G60, similar in pattern to that of A. C. (6) Persisting T.N.R. in presence of distracting visual stimulus in infant G. 47, age 12 weeks. (7) Alternating T.N.R. in infant A. R., age 16 weeks, induced by visual stimulus. (8) Postural bilateral symmetry in infant G48, age 20 weeks, superseding T.N.R.

throughout most of the first year of life.* This infant spent approximately one-half of the 834 seconds of cinematically recorded behavior up to the eighty-second day in T.N.R. Sixty-five separate T.N.R.'s were observed; only one of these was leftward.

Fig. 5 graphs the incidence of these T.N.R.'s which fell to zero on the nineteenth day, when the head preferred a mid-position and the arms assumed more symmetric and versatile attitudes.

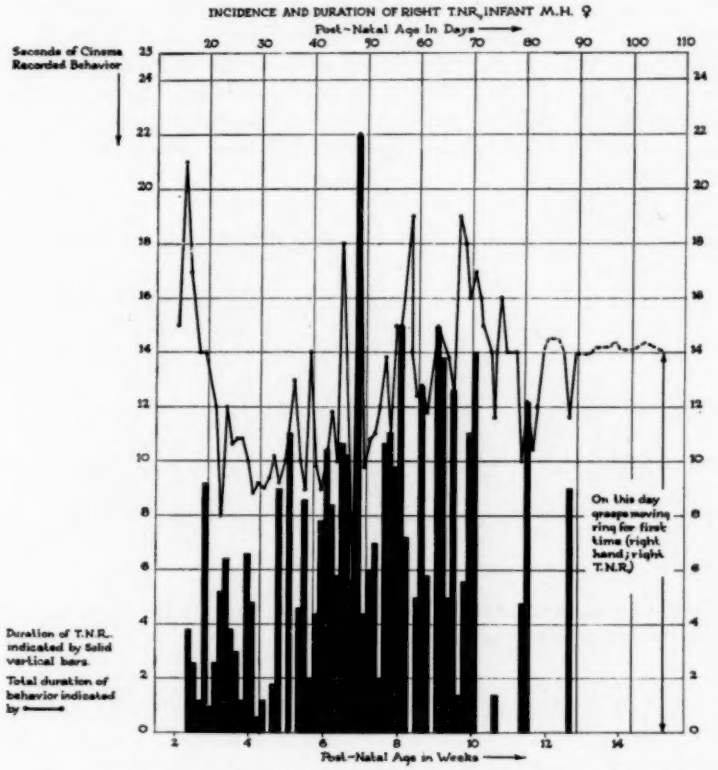
INCIDENCE AND DURATION OF RIGHT T.N.R. INFANT M.H. ♀
Post-Natal Age in Days
20 30 40 50 60 70 80 90 100 110
Seconds of Cinema Recorded Behavior
25 24 22 20 18 16 14 12 10 8 6 4 2 0
On this day grasps moving ring for first time (right hand; right T.N.R.)
Duration of T.N.R. indicated by Solid vertical bars.
Total duration of behavior indicated by
2 4 6 8 10 12 14
Post-Natal Age in Weeks

Fig. 5.—Graph showing the duration and incidence by ages of the right T.N.R. in infant M. H. between 2 and 16 weeks of age.

The submergence of the naïve T.N.R. of early infancy is the result of the ascendancy of cortical controls, probably in the motor and premotor regions, if Bieber and Fulton's data, regarding ablation, for monkeys and baboons apply to man.[2] This probability is strengthened by our findings in a case of cerebral palsy, in which necropsy (at the

*These observations were incidental to a study, with H. M. Halverson, of the visual and postural reactions of an infant to three interlocked rings, red, white, and blue, 4 cm. in diameter. The infant (M. H.) lay supine in a small photographic cubicle. The rings within easy reach were suspended on a horizontal string above her head and slowly moved left and right across the field of vision.

age of 14 years) revealed a severe but uncomplicated birth lesion of the basal ganglia (status marmoratus) (Fig. 6).[3] The boy in question, A. C. was afflicted with extreme double athetosis and, although intelligent, could not sit, walk, talk, grasp, or even hold up his head sustainedly. Cinema records of his spontaneous behavior in the supine position were made at the age of 7 years. Subjected to frame-by-frame analysis, these records revealed temporal and spatial patterns remarkably similar to those of the activated T.N.R. of normal infancy. Fig. 7 portrays eleven comparable phases in the arm and head movements of the palsied boy, aged 7 years, and of a normal infant, 4 weeks old.

These phases may be envisaged as a slashing windmill reaction emerging out of and returning to a basic T.N.R. attitude. The presence of the T.N.R. was obscured by lively athetotic movements, but when the cinema films were quantitatively studied, it was found that this boy

Fig. 6.—Microphotographic section of a birth lesion of the basal ganglia of A. C. (Status marmoratus of lenticulate and thalamic nuclei.) The marblelike appearance is produced by patches of gliosis and delicate myelin fibers in a striation which is nearly completely lacking in ganglion cells.[3]

was in a T.N.R. posture from 41 to 56 per cent of the recorded time at 7, 10, and 13 years of age. The head generally took the lead in initiating the T.N.R. attitude. In no instance was a reversed T.N.R. attitude (head averted to one side with the arm of that side flexed) assumed even momentarily. All this suggests that the proprioceptive stimulus in the neck was operating to bring about the natural reflex.

Although the T.N.R. is a normal and prominent feature of early infant behavior, it becomes a pathologic symptom if it persists with undue dominance beyond the age of 6 months. In cases of cerebral palsy such persistence may usually, if not always, be taken as a prognostic sign that the child will never acquire the ability to walk. In primary and secondary amentia the T.N.R. may persist for many months as an evidence of slowed down or arrested development. We refer here to spontaneous manifestations of the T.N.R. which may be naturalistically

observed while the child lies supine, either quiescent or in general postural activity. In some instances, as already suggested, it is possible to induce the T.N.R. indirectly by slowly moving a stimulus across the field of vision, thereby inducing head rotation. In aments of lower grade, and in certain neurological conditions, the examiner is able to elicit the T.N.R. response by forcible or passive rotation of the head. In normal infants, however, such attempted manipulation by the examiner arouses resistance reactions. This is probably the reason Magnus failed to find the T.N.R. in the absence of abnormality.

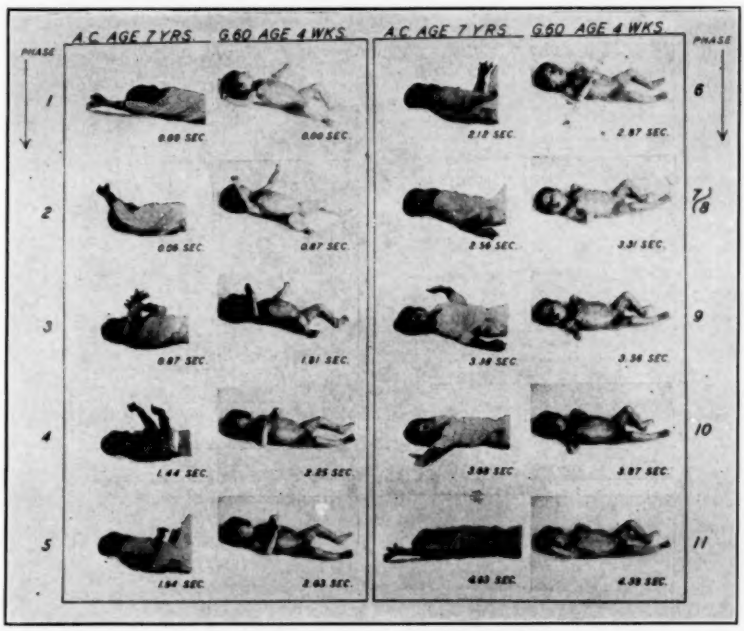

Fig. 7.—Comparative consecutive phases of the athetotic action pattern of A. C., aged 7 years, and of the spontaneous supine action pattern of a normal infant, G60, aged 4 weeks. Eleven phases, with the elapsed time indicated in seconds, are shown side by side in vertical columns. These phases may be envisaged as a slashing windmill reaction emerging out of and returning to a basic T.N.R. attitude.

When a large number of normal infants are examined at intervals during the first three months, we find that at least one-third consistently assume a right T.N.R.; possibly a third, the left T.N.R.; and the remainder adopt either right or left in a somewhat ambivalent manner. These figures are crude (the problem needs refined study), but they suggest important trends and individual differences in the genesis of laterality. Handedness is a partial and sometimes a misleading index of physiologic unilaterality. It is probable, however, that emphatic, constitutional left handedness is correlated with a strong infantile left T.N.R.

In our normative survey of the ontogenetic sequences of behavior pattern, from twenty-six to forty-nine infants were examined at lunar month intervals up to the age of 56 weeks.[4] It is a remarkable fact that 100 per cent of the infants at 4 weeks of age, when observed in a free supine posture, spontaneously maintained the head predominantly rotated to one side; 100 per cent likewise held their arms in characteristic T.N.R. attitudes. We conclude that the T.N.R. is a normal and virtually universal feature of neonatal infancy. Indeed, for 8 weeks the T.N.R. holds strong sway; at 12 weeks it is less conspicuous; at 16 weeks it is in transition; at 20 weeks, in eclipse, for at 20 weeks 100 per cent of our normative infants maintained the head in mid-position. And when the head is predominantly held in mid-position, at least one-half of each

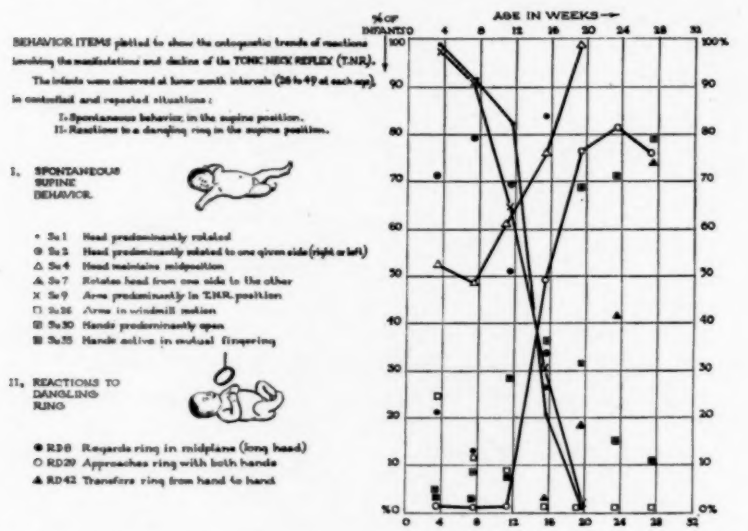
% OF INFANTS
AGE IN WEEKS
BEHAVIOR ITEMS plotted to show the ontogenetic trends of reactions involving the manifestations and decline of the TONIC NECK REFLEX (T.N.R.).
The infants were observed at lunar month intervals (26 to 49 at each age), in controlled and repeated situations:
I. Spontaneous behavior in the supine position.
II. Reactions to a dangling ring in the supine position.
I. SPONTANEOUS SUPINE BEHAVIOR.
• Su 1 Head predominantly rotated
⊕ Su 2 Head predominantly rotated to one given side (right or left)
△ Su 4 Head maintains midposition
▲ Su 7 Rotates head from one side to the other
X Su 9 Arms predominantly in T.N.R. position
□ Su 26 Arms in windmill motion
⊠ Su 30 Hands predominantly open
■ Su 33 Hands active in mutual fingering
II. REACTIONS TO DANGLING RING
● RD 8 Regards ring in midplane (long head)
○ RD 29 Approaches ring with both hands
▲ RD 42 Transfers ring from hand to hand

Fig. 8.—Graph showing the ontogenetic trends of the components of the tonic neck reflex.[4]

T.N.R. subsides, and tonic symmetry displaces tonic neck asymmetry. The ontogenetic trends which underlie these transformations of postural pattern are plotted in Fig. 8.

The process of transformation is extremely complex. It is not a process of simple substitution but one of progressive interlocking, so that neither symmetry nor asymmetry gains permanent or complete ascendancy. It implies an intricate neurological cross-stitching which organizes antagonistic muscles and unilateral functions into reciprocal relationships. The addiction of the young infant to T.N.R. postures is both a symptom and a condition of his behavior growth. The infantile T.N.R. represents a morphogenetic stage in which fundamental neurological coordinations are laid down to form the framework for later

postural, manual, locomotor, and psychomotor reactions. Indeed, the T.N.R. is part of the ground plan of the organism pervasively identified with its unitary, total action system.

The T.N.R. accordingly has an ecology. More or less directly it subserves adaptations to the environment, prior to birth as well as later. The T.N.R. helps the fetus to accommodate to the conformation of the uterine cavity; and it may even facilitate the longitudinal presentation and orientation of the fetus at the entrance of the birth canal. The T.N.R. of the neonatal infant is well suited to postural attitudes which the child needs to assume when suckled at the breast. The activated windmill T.N.R. of the early weeks with its intensification of grasp responses suggests vestiges of arboreal groping and clinging. But the future and formative references of the T.N.R. are more significant. The T.N.R. attitude promotes and channelizes visual fixation by the infant on his extended hand; it leads to hand inspection, to eye-hand coordinations, to prehensory approach, and eventually to unidextrality. It contributes to the organization of the diagonal reflexes of prone locomotion. It reduces the hazard of suffocation to the infant and is well adapted to acts of rejection and withdrawal. Elaborated and inflected, it finally figures in innumerable adult acts of skill, aggression, and extrication. Attitudinal asymmetry always remains in reflex reserve, as well as subject to voluntary mobilization.

Man does not face the world on a frontal plane of symmetry, but at an angle, and he makes his escapes obliquely! This orientation is prefigured in the T.N.R. attitude of infancy. The bias is grounded in the primitive anatomy of the nervous system and entails such elaborate present and future ramifications that much developmental time is needed to mature the neuromotor structure. For such morphogenetic reasons the T.N.R. is a prolonged and conspicuous feature of the early patterning of human behavior. For the same reasons the T.N.R. is a diagnostic indicator of development status and a clinical sign of neurological defects.

SUMMARY

1. The tonic neck reflex (T.N.R.) is an asymmetric postural attitude, so basic that it is found in lower animals as well as in man. It involves the total action system, but particularly arms and head.

2. It is a normal characteristic of the human infant during the first 12 weeks of waking life, spontaneously manifested in the supine position. At 20 weeks it is normally supplanted by symmetric head and arm postures.

3. Marked persistence of the T.N.R. beyond the first half year is indicative of retarded, arrested, or defective development.

4. In association with basal ganglion lesions it is a prognostic indication that the child will not "learn" to walk.

5. The T.N.R. is a natural but not a stereotyped reflex. It undergoes progressive growth changes. It serves useful adjustments in the fetus as well as the infant in neonatal life. It is morphogenetically so fundamental that it has clinical value both as an index of maturity and as a symptom of neurological abnormalities.

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THE USE OF HONEY AS A CARBOHYDRATE IN INFANT FEEDING

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ALTHOUGH honey has been known as a food from the earliest days of which we have historical record, its importance to man seems to have decreased as civilization has advanced. In view of the fact that honey is a product occurring free in nature ready for use without artificial treatment and that it is composed of two monosaccharides most acceptable to the organism, it is strange that honey has not enjoyed wider use, especially in the feeding of infants and children.

The composition of honey has been reported by Browne, in 1908, as follows: water, 17.70 per cent; sucrose, 1.90 per cent; levulose, 40.50 per cent; glucose, 34.02 per cent; dextrin, 1.51 per cent; ash, 0.18 per cent.

Luttinger, in 1922, published values for honey constituents comparable to the figures quoted from Browne except for a slightly higher ash content. Luttinger also included figures for acetic, malic, and formic acids, the content of these being 0.2, 0.3 and 1.1 per cent, respectively.

The mineral value of honey has been studied more in detail by Schuette and Remy (1932). They found dark honeys to be superior and reported the following results in milligrams of mineral per kilogram of honey:

Table I

	LIGHT HONEYS			DARK HONEYS		
	MIN.	MAX.	AV.	MIN.	MAX.	AV.
Iron	1.20	4.80	2.40	0.70	33.50	9.40
Copper	0.14	0.70	0.29	0.35	1.04	0.56
Manganese	0.17	0.44	0.30	0.52	9.53	4.09

Thus honey is seen to contain valuable minerals in amounts large enough to be significant in infant feeding.

In addition to the carbohydrates, acids, and minerals, Luttinger believed vitamins A, B, C, and D also to be present in honey in appreciable amounts. Other workers (notably Dutcher, 1918; Hawk, Smith, and Bergeim, 1921; Scheunert, Schlieblich, and Schwanebeck, 1923; and Hoyle, 1929) have not been able to confirm the presence of these vitamins in honey except in perhaps negligible quantities. It may be

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that different sources for honey affect its composition sufficiently to account for the different results reported by these workers.

The best reports in the literature regarding the use of honey come chiefly from European sources, although Luttinger, in 1922, had advocated its use in the United States. Luttinger summarized historical and literary references to honey and commented upon its ease of digestion, good utilization, and valuable mineral and vitamin content. His conclusion that honey was an excellent source of carbohydrate for infants was based on 419 feeding cases, but he did not report any details for his work. Comby in 1926 gave a brief review and praised the use of honey for infants because its aseptic nature made it an excellent and safe source of minerals and vitamins for addition to pasteurized milk. Comby, however, like Luttinger, included no experimental data in his paper.

In 1931 two papers based on carefully controlled experiments were presented by Lahdensuu and Muniagurria. Lahdensuu reported twenty cases in which honey had been alternated with saccharose as a supplement to milk. The honey feedings gave better weight gains than did the saccharose, although they contained fewer calories per unit amount of feeding. Lahdensuu believed the natural form of the sugars in honey somehow enabled the body cells to bind water to better advantage and thus facilitate gain in weight. Lahdensuu commented on the good digestion which accompanied the feeding of honey. Diarrhea and vomiting were decreased, presumably because the natural sugars of honey were easily and quickly digested and the natural acids aided the digestion of milk. Lahdensuu also made blood sugar tolerance studies comparing saccharose with honey and found the blood sugar rose more rapidly and to higher levels following honey administration than after saccharose. No glycosuria, however, occurred as a result of the higher levels of blood sugar, nor was acidosis observed in the urine.

Muniagurria, in the introduction to his paper on honey, discussed the conditions required for a carbohydrate to be suitable for infant feeding. He evaluated honey and compared it with other common sources of carbohydrates, using case reports to illustrate his various points. His major conclusion was that honey was not laxative per se, but because of the completeness and ease with which it was digested it corrected conditions which had caused constipation when other less easily digested carbohydrates had been fed. He found honey especially suited to cases of dystrophy and also obtained good results with honey therapy for enterocolitis. Muniagurria stated that honey, by improving digestion, could correct dyspeptic states as effectively as did Finkelstein's protein milk. He tested his hypothesis by feeding relatively large quantities of honey, adapting the treatment to individual needs and increasing honey feedings from low initial amounts up to 40 or 50 gm. per kilogram of body weight.

Stancanelli (1933), following the suggestions of Muniagurria, also used honey successfully in the treatment of dystrophy. He reported fourteen cases in which favorable clinical effects had resulted from the substitution of honey for dextrimaltose. The infants made regular gains in weight following the introduction of honey into their formulas.

Following the work of Emrich who had increased the rate of growth of older children by means of honey administration, Rolleder (1934) gave two tablespoons of honey daily, in addition to the regular diet, to a group of twenty-nine school boys. His control group of twenty-nine was carefully paired for both age and weight with the individuals in the honey group. The boys receiving honey were superior at the end of six weeks not only because of greater weight gains but also because of increases in hemoglobin.

Farioli (1936) has made the most thorough recent study in regard to the use of honey for infants. The eighteen infants in his case reports ranged in age from 10 days to 16 months, and suffered from a variety of disorders, such as rickets, enteritis, malnourishment, and prematurity. He was able to confirm the opinions of former observers since he found excellent tolerance for honey as demonstrated by the good weight gains and well-being of his infants. Farioli studied particularly the fecal flora and observed a shift during honey administration from gram-negative to gram-positive bacteria. In blood sugar tolerance tests he found no excessive elevation of the blood sugar following honey ingestion.

From the above review of the literature it would appear that honey, because of its ease of digestion, its ability to control diarrhea, its favorable effect upon weight gains, and its normal intermediary metabolism, might have special advantages as a carbohydrate for use in infant feeding.

EXPERIMENTAL PROCEDURE AND DISCUSSION

In order to investigate the suitability of honey for infant feeding it was used under controlled conditions for ten healthy male infants who had been admitted to the hospital for various metabolism studies. Most of the infants were about 1 month of age or less on admission, and all were normal in every respect. Seven of the ten infants were studied until they were about 6 months old. Throughout the study the infants were fed either evaporated milk, one-half skimmed dried milk, or one-half skimmed lactic acid powdered milk* The source of carbohydrate was either honey† or karo corn syrup. In addition, solutions of ferric pyrophosphate, copper sulphate, thiamin, cevitamic acid, and crystalline vitamin D were used in the formulas at different levels. Table II

*These milks were furnished through the courtesy of Irradiated Evaporated Milk Association, The Borden Company, and Mead Johnson & Company.

†Honey, carefully selected as to source, purity, and uniformity, was supplied by the Lake Shore Honey Company, Chicago.

TABLE II

NAME	BIRTH	AGE DURING HOSPITALIZATION	MILK	CARBOHYDRATE	WEIGHT	
					INITIAL	FINAL
John	8/31/36	4 wk.—5½ mo.	Evaporated	Karo-honey	3650	7325
Hal	10/7/36	7 wk.—6 mo.	Evap.-Dryco	Honey	3535	7030
Rob	1/18/37	18 da.—7 wk.	Evaporated	Honey	3660	4515
Bart	2/17/37	18 da.—5 mo.	Dryco	Honey-karo-honey	3365	6770
Myles	8/19/37	19 da.—6½ mo.	Dryco	Honey-karo-honey	3170	7320
Ned	9/3/37	14 da.—6½ mo.	Dryco	Honey-karo-honey	3170	6770
Kermit	11/5/37	6 wk.—2½ mo.	Skim lactic acid powdered (½)	Karo	3850	4600
Ray	12/1/37	7 wk.—3½ mo.	Dryco	Karo	4180	5810
Noel	12/19/37	4 wk.—5½ mo.	Dryco	Honey	2895	7710
Jack	2/18/38	4 wk.—3¼ mo.	Dryco	Honey	3004	5680

gives the birth dates, the duration of hospitalization, the type of formula, and the initial and final weights for each infant.

Since the number of stools per day is one indication of an infant's well-being, careful records were kept by the nurses in charge of the infants. To facilitate analysis and charting of results the average number of stools per day was calculated for each period during which no changes were made in an infant's formula. These data are presented in Fig. 1. It will be observed that in general all of the infants maintained an average of less than two stools per day. The chief exceptions

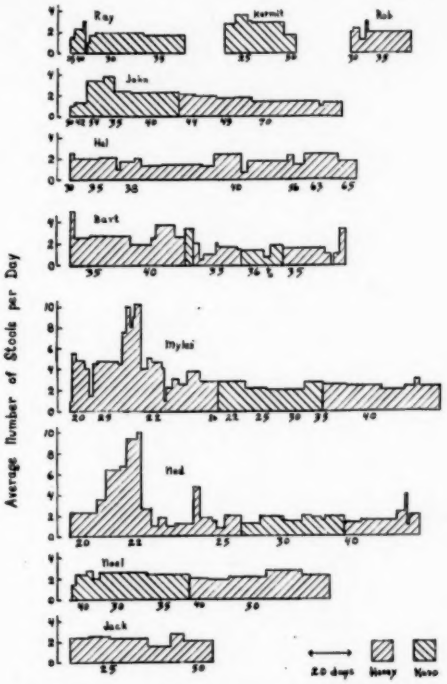

Fig. 1.—Average number of stools per day for consecutive periods during which formulas remained unchanged. Small numbers indicate grams of carbohydrates per day for each period.

to this were in infants less than 2 months of age, who sometimes averaged between two and three stools per day. In only two cases did a definite diarrhea occur, and with each of these infants the diarrhea was brought under control by use of boiled skim milk without omitting the honey from the feedings. It may, therefore, be concluded that honey was well tolerated by these infants.

In addition to the average number of stools per day recorded in Fig. 1, the type of carbohydrate for each period is included in the graph, together with the number of grams of carbohydrate in the formula per

day. When results with karo corn syrup and honey were compared for infants of similar ages, or for older infants who received first one and then the other of these two carbohydrates, but little difference in number of stools per day was noted. The level of carbohydrate was altered from time to time in order to maintain a proper soft consistency for the stools. Individual infants varied in this respect, some requiring more and some less of the karo or honey. The role of the carbohydrate ap-

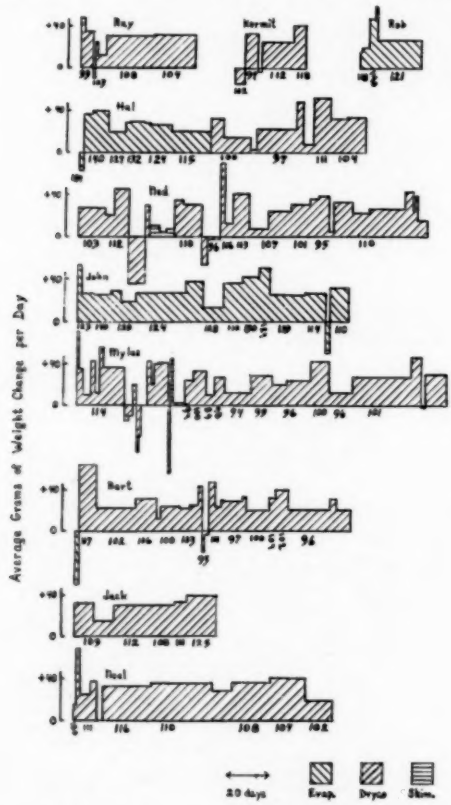

Fig. 2.—Average weight changes per day for consecutive periods during which formulas remained unchanged. Small numbers indicate calories per kilogram per day for each period.

peared to be that described by Muniagurria, since increases of honey apparently relieved constipation by improving digestion without causing a diarrhea. Honey may thus have a distinct advantage in infant feeding over those carbohydrates which have a tendency to be laxative.

Another means of evaluating the utilization of honey by the infants was found in the daily weight records. In order to show the regularity with which weight gains were maintained, the average gain or loss

per day has been calculated for each period of days during which the infant's formula remained unchanged. These weight changes are plotted in Fig. 2. The only weight losses of consequence occurred with the two infants who each had a short period of diarrhea. Other than these two periods, during which an infection may have caused the digestive disturbance, weight gains were quite consistently maintained at about 20 to 30 gm. per day.

Since weight gains are, to a large extent, controlled by the energy value of the ingested food, the average caloric intake per kilogram of body weight has been calculated for each period for each infant and is included in Fig. 2. In Fig. 3 these caloric intakes have been plotted

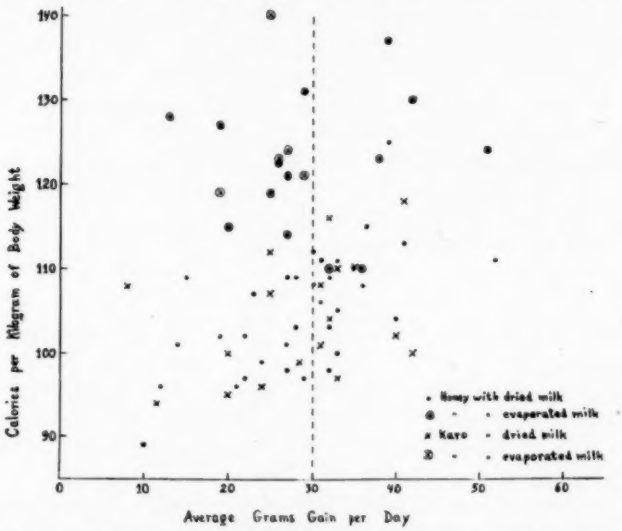

Fig. 3.—Relation of calorie intake and type of milk and carbohydrate to gain in weight.

against the average weight gains for all periods during which an infant's formula had remained unchanged for at least a week.

Although weight gains are always under the influence of a number of related factors besides the caloric intake, there was a tendency for slightly greater weight gains to occur with those infants receiving honey instead of karo. This was most noticeable when these two carbohydrates were contrasted as supplements to evaporated milk. Out of a total of thirty-seven periods during which the infants averaged less than 30 gm. gain per day, honey had been fed in 65 per cent of the cases. On the other hand, with average weight gains above 30 gm. per day, honey had been fed in 71 per cent of the thirty-four cases. When just the evaporated milk feedings were considered, honey had been fed in 62 per cent of the cases gaining less than 30 gm., while it had been used for 100 per

cent of the cases gaining more than 30 gm. It would seem that honey, at least to a moderate extent, had facilitated higher weight gains.

Another means of evaluating the utilization of honey by infants has been a series of blood sugar tolerance tests which have been conducted on these infants. In these tests, the details of which are being published in another paper (Schlutz and co-workers, 1938), various sugars which are commonly used in infant feeding were administered in 20 per cent solutions and blood sugar determinations made at the end of 15, 30, 60, 90, and 120 minutes. Honey appeared to have special advantages for infants because, with the exception of dextrose, it was absorbed most quickly of all the sugars tested during the first fifteen minutes following ingestion, yet did not flood the blood stream with exogenous sugar. It also maintained both a steady and a slow decrease in blood sugar until the fasting level was again reached. This response of honey is presumably due to the unique combination of the two easily digested monosaccharides, dextrose and levulose. Honey is quickly digested and absorbed into the body because if its dextrose content, while the levulose, being somewhat more slowly absorbed, is able to maintain the blood sugar. Honey has an advantage over sugars which contain higher levels of dextrose since it does not cause the blood sugar to rise to higher levels than can be easily cared for by the body.

SUMMARY

Ten healthy male infants have been studied during the first 6 months of their lives for a total of 151 weeks. Formulas for all infants were restricted to either evaporated or dried milk and carbohydrate, with additional supplements of pure vitamin or mineral solutions. The response of the infants to honey as a source of carbohydrate has been contrasted with their response when receiving karo corn syrup.

The general well-being of the infant, the number of stools per day, and weight gains have been used to determine the value of honey in regular feedings. Besides these criteria, blood sugar tolerance studies have been employed to contrast the response to honey with that resulting from administration of other common sources of carbohydrate.

From these studies it is concluded that honey is easily digested, being absorbed more rapidly than most sugars during the first fifteen minutes after ingestion. It is well tolerated by the infant and does not cause diarrhea. It may facilitate weight gains, since there was a slight tendency for greater average gains per day to occur on lower calorie intakes when honey was included in the formulas.

It would seem, therefore, that honey is a type of carbohydrate which is well suited to the infant's needs and probably should be recommended for wider use in infant dietaries.

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STATISTICAL STUDIES ON PREMATURITY

I. The Incidence of Prematurity and the Effect of Certain Obstetric Factors

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IN 1932 during the course of an analysis, "The age distribution of 15,370 obstetric patients and its effect upon the type of delivery," the author recorded the births of 974 infants who had been classified as premature. This study included only patients delivered of viable babies, while all those having abortions, i.e., fetuses less than 1500 gm. in weight and less than 35 cm. in length, were omitted from the series. The infants termed premature had reached the above standards either in weight or length or both but weighed less than 2500 gm. and were less than 45 cm. long. All others were classed as "full term." This arbitrary standard for abortion and prematurity has long been used in the Obstetrical Department of the Johns Hopkins Hospital, whence came the above series of cases. The 974 premature infants made up 6.34 per cent of the total cases, and the incidence in white and colored women was 4.75 and 7.97 per cent, respectively.

It has frequently been noted in the clinic that whereas almost all infants whose length is less than 45 cm. are less than 2500 gm. in weight, a considerable number are seen with a birth weight between 2000 and 2500 gm. but measuring 45 to 47 cm. in crown-heel length. It was decided to examine the punch card abstracts of the case records for the clinic, both hospital and outside services, in order to determine how many babies there were who, while above the standards for abortion, were below the individual weight and length criteria for full term. Such a series of cases would enable the derivation of both weight and length incidences of prematurity for contrast with the previously mentioned one. Also it would be possible to determine the effect of certain obstetric factors such as race, age, and parity of the mother upon these incidences.

Gross Incidence.—A total of 39,394 deliveries of theoretically viable children occurred in the hospital and outside obstetric services from the beginning of the department in 1896 to Jan. 1, 1936. Among these there were 4,055 infants weighing less than 2500 gm., yet at least 35 cm. in length. This number includes certain very small children weighing less than 1500 gm., yet 35 cm. or more in length and hence technically classified as "premature." It does not include fetuses below the premature

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standard in both weight and length. Also included in the series are a considerable number of infants whose birth weight was below 2500 gm. yet whose length was 45 cm. and over, hence, who had been catalogued as full term. In other words, excluding abortions, this series includes all infants premature according to weight alone at birth.

In a similar fashion a second series of babies was accumulated, including all whose length at birth was less than 45 cm., but excluding fetuses below the premature standard in both length and weight. This series corresponds in all respects to the former except that here the prematurity is decided according to length instead of weight. It was of interest and, in our opinion, of considerable significance that while 4,055 infants were found whose weight at birth was less than 2500 gm., only 2,415 were delivered who were less than 45 cm. in length. The make-up of these series, subdivided according to race, together with the incidences for prematurity derived, are shown in Table I. Since small babies

TABLE I

THE INCIDENCE OF PREMATURITY, ACCORDING TO VARIOUS WEIGHTS AND LENGTHS

	NUMBER OF INFANTS			PER CENT OF TOTAL DELIVERIES		
	WHITE	BLACK	TOTAL	WHITE	BLACK	TOTAL
Single Births						
Total viable deliveries	18,375	20,569	38,944	100.00	100.00	100.00
Less than 2500 gm.	1,120	2,458	3,578	6.10	11.95	9.19
Less than 2400 gm.	929	2,048	2,977	5.06	9.96	7.64
Less than 2300 gm.	781	1,692	2,473	4.25	8.23	6.35
Less than 2200 gm.	637	1,348	1,985	3.47	6.55	5.10
Less than 2100 gm.	525	1,134	1,659	2.86	5.51	4.26
Less than 2000 gm.	429	902	1,331	2.33	4.39	3.42
Less than 1500 gm.	148	315	463	0.81	1.52	1.19
Less than 1000 gm.	26	33	59	0.14	0.16	0.15
Less than 45 cm.	666	1,496	2,162	3.62	7.27	5.55
Less than 44 cm.	447	1,033	1,480	2.43	5.02	3.80
Less than 43 cm.	316	752	1,068	1.72	3.66	2.74
Less than 42 cm.	238	527	765	1.30	2.56	1.96
Less than 41 cm.	183	386	569	1.00	1.88	1.46
Less than 40 cm.	129	259	388	0.70	1.26	1.00
Less than 35 cm.	12	13	25	0.07	0.06	0.06
Multiple Births						
Total viable twins	426	474	900	100.00	100.00	100.00
Less than 2500 gm.	190	287	477	44.60	60.55	53.00
Less than 2000 gm.	82	137	219	19.25	28.90	24.33
Less than 1500 gm.	27	59	86	6.34	12.45	9.56
Less than 1000 gm.	7	11	18	1.64	2.32	2.00
Less than 45 cm.	86	167	253	20.19	35.23	28.11
Less than 40 cm.	18	42	60	4.23	8.86	6.67
Less than 35 cm.	3	8	11	0.70	0.17	1.22

occur much more frequently in multiple than in single births these have been analyzed separately in order to determine a more exact incidence. Omitting twins from consideration it will be noted that the delivery of infants weighing less than 2500 gm. occurred 3,578 times, while only 2,162 were found who were less than 45 cm. in length. Moreover, there

were 463 premature infants weighing less than 1500 gm. and 59 less than 1000 gm., but all at least 35 cm. in length. In contrast, however, only twenty-five children were found less than below 35 cm. but weighing at least 1500 gm. The total incidence of prematurity according to weight was 9.19 per cent, while for length it was only 5.55 per cent. A weight incidence comparable to 45 cm. length fell between 2200 and 2300 gm. An interesting feature of Table I is the racial disparity which was noted, showing that the incidence for the various weights and lengths in colored infants was almost twice as great as for white. Of all white infants delivered 6.1 per cent weighed less than 2500 gm., while a similar incidence for blacks fell between 2100 and 2200 gm. Similarly, 3.62 per cent of white children were less than 45 cm. long and the corresponding black rate was approximately at 43 cm. Whether these figures indicate a true racial difference in incidence of prematurity or whether different criteria are necessary for the two races will be discussed in a subsequent paragraph.

That portion of Table I dealing with multiple births was computed according to the same weight and length specifications as was used in the analysis of deliveries of single children. It will be noted that over one-half of all viable twin infants weighed less than 2500 gm. and more than a quarter were under 45 cm. in length. A similar racial difference in incidence was found as has been described for single births. Judging by weight alone prematurity occurred almost six times as often in twin deliveries, while for length a five to one ratio was observed. It is of interest in this connection to note the disparity between the numbers of first and second twins upon such division of the total premature multiple births. A definite tendency for the heavier child to be born before the lighter one was indicated by the following number of infants under 2500 gm. in birth weight: 219 (first born) and 258 (second born). No similar difference was noted, however, in the comparative series selected according to total length.

Age.—It is generally stated that the likelihood of premature delivery is increased by excessive multiparity, as well as through too closely spaced childbearing. If this is so, one would expect the incidence of prematurity to increase with advancing age of the mother. Table II indicates the proportion of those small infants under analysis (both weight and length series) according to several age groups for the mothers, and for comparison there is submitted the age distribution of the patients making up the general clinic population. No significant difference in incidence was found for the three groups, although certain rather suggestive discrepancies were noted. First, 33.66 per cent of the total deliveries occurring on the service were in women less than 20 years old, while 37.70 per cent of the infants weighing less than 2500 gm. and 30.04 per cent of those less than 45 cm. in length fell in the same cate-

TABLE II

THE EFFECT OF AGE OF MOTHER UPON THE INCIDENCE OF PREMATURITY

AGE	PER CENT OF TOTAL					
	WEIGHT				LENGTH UNDER 45 CM.	GENERAL CLINIC POPULATION
	— 1499 GM.	1500-1999 GM.	2000-2499 GM.	TOTAL		
16 and under	7.43	9.82	9.39	9.26		7.41
17 to 19	21.67	23.87	31.39	28.44		26.25
20 to 24	32.20	29.00	29.24	29.53		33.08
25 to 29	18.27	13.60	13.18	13.88		16.49
30 to 34	10.84	10.27	8.65	9.30		9.23
35 to 39	5.88	10.27	6.56	7.37		5.53
40 and over	3.72	3.17	1.58	2.22		2.01
19 and under	29.10	33.69	40.78	37.70	30.04	33.66
20 to 34	61.31	52.87	51.07	52.71	59.54	58.80
35 and over	9.60	13.44	8.14	9.59	10.41	7.53

gory. We would interpret this to indicate that early childbearing does not increase the incidence of true premature birth, but rather that the young woman at term gives birth to an infant smaller in weight but equal in length to that of the more mature individual. Furthermore, it would seem that this small child is more vigorous and stands a better chance of survival than does one of the same weight born to an older woman. Further analysis would seem to substantiate these statements, as the percentage of infants 2000 to 2499 gm. to the total number of infants less than 2500 gm. was found to decrease with advancing age of the mother. Thus for the age group 17 to 19, 68.22 per cent of the total number of infants less than 2500 gm. weighed between 2000 and 2499 gm., while for the group aged 40 years and over a similarly calculated rate of 47.62 per cent was obtained. Finally, from Table II we obtained suggestive evidence of an increased incidence of prematurity in women aged 35 years and older, and found in this age group 7.53 per cent of the patients comprising the general clinic population as contrasted with 9.59 and 10.41 per cent of the total prematures as determined by weight and length, respectively.

Parity.—In view of what has been said concerning the effect of age of mother upon the incidence of small infants, it was not surprising to find that primiparous births made up a larger proportion of the total in both the weight and length (premature) series as contrasted with the general clinic population. This is illustrated by Table III. Furthermore, the comparative incidence of premature births was less for each group with parity more than one, except for the group para x and over, for weight, and the group para viii and over for length, where practically identical incidences obtained. As was stated under the discussion of age, we do not believe that the large number of small children born to primiparas represents a true index of prematurity, but

rather that this group, particularly if young, tends to give birth to relatively undersized but essentially mature infants. Moreover, it is known that each successive child tends to be larger than the one before. This may explain the low incidence of infants weighing less than 2500 gm. found in our series as contrasted with the general clinic population for the higher para groups. This had been a somewhat surprising finding, since it is in this type of patient that certain obstetric complications predisposing to premature delivery, such as placenta previa, premature separation, chronic nephritis, etc., are most likely to occur. Moreover, the incidence of twins increases with the parity of the mother. In this bracket no figures are available for the effect of increasing weight or length as analyzed under the heading "age."

TABLE III

THE EFFECT OF PARITY OF MOTHER UPON THE INCIDENCE OF PREMATURITY

PARITY OF MOTHER	PER CENT OF TOTAL								
	WHITE			BLACK			TOTAL		
	GENERAL CLINIC POPULATION	WEIGHT LESS THAN 2500 GM.	LENGTH LESS THAN 45 CM.	GENERAL CLINIC POPULATION	WEIGHT LESS THAN 2500 GM.	LENGTH LESS THAN 45 CM.	GENERAL CLINIC POPULATION	WEIGHT LESS THAN 2500 GM.	LENGTH LESS THAN 45 CM.
1	36.64	46.28	41.44	35.16	43.89	37.32	35.87	44.65	38.60
2	18.67	13.95	13.44	21.24	20.56	21.46	20.01	18.47	18.97
3	11.55	9.77	10.89	12.34	8.89	10.51	11.96	9.17	10.63
4	8.54	7.69	9.34	8.32	6.84	7.90	8.43	7.11	8.34
5	6.16	5.93	6.36	5.91	5.02	5.80	6.03	5.31	5.97
6	4.95	3.84	3.82	4.60	3.79	4.01	4.77	3.80	3.95
7	4.21	3.34	3.11	3.26	2.94	3.31	3.72	3.06	3.25
8	2.93	2.09	2.69	2.53	2.43	2.99	2.72	2.32	2.90
9	2.06	1.75	2.40	1.81	1.47	1.97	1.93	1.56	2.11
10 and over	4.27	5.34	6.51	4.82	4.17	4.71	4.56	4.54	5.27

Rupture of Membranes.—Labor before term is preceded often by premature rupture of the membranes, and accordingly the series under discussion was analyzed in order to determine how often this accident occurred and to contrast its frequency with that pertaining for the general clinic population of term deliveries. The results of this analysis are shown in Table IV. It will be seen from this table that rupture before the onset of labor was observed somewhat more frequently with prematurity than at term, but the difference amounted to only 3 per cent and was considered insignificant. It is interesting to note, furthermore, that the time of rupture was almost identical in the two series analyzed according to weight and length, respectively.

TABLE IV

THE TIME OF RUPTURE OF MEMBRANES IN PREMATURE LABOR

	PER CENT OF TOTAL		
	GENERAL CLINIC POPULATION	WEIGHT LESS THAN 2500 GM.	LENGTH LESS THAN 45 CM.
Before onset of labor	17.14	20.22	18.73
First stage	32.66	17.61	17.70
Second stage	50.20	62.17	63.58

Maternal Complications.—The incidence of certain maternal complications predisposing to premature labor, either spontaneous or induced, is shown in Table V. A positive Wassermann was noted four and one-

TABLE V

THE INCIDENCE OF SOME MATERNAL COMPLICATIONS PREDISPOSING TO PREMATURE DELIVERY

COMPLICATION	PER CENT OF TOTAL			
	WEIGHT LESS THAN 2500 GM.			GENERAL CLINIC POPULATION
	WHITE	BLACK	TOTAL	
Syphilis	4.66	21.35	16.07	2.55—White 20.76—Black
Heart disease	3.33	1.58	2.13	0.57
Eclampsia	4.91	2.43	3.21	0.70
Other toxemia	18.06	10.75	13.06	14.01
Placenta previa	4.49	1.58	2.50	0.76
Premature separation	2.91	1.62	2.03	0.52
Prolapse of cord	1.33	1.00	1.11	—
Total	39.69	40.31	40.11	

half times as often in the colored as in the white patient. As contrasted with the general clinic population, syphilis was found more frequently in the white, but about equally often in the colored woman delivering prematurely. Heart lesions, eclampsia, premature separation, and placenta previa had a much higher incidence in the premature series. In about 40 per cent of the cases some maternal complication was found which might possibly have contributed to the early termination of the pregnancy. It is interesting to note that the incidence of total complications was approximately the same in the black and white, the high rate of syphilis in the former group being compensated for by a disparate number of other complicating factors in the latter. In other words, omitting cases with maternal complications, there remained the same preponderance of colored over white infants in the series.

The figures given in Table V were obtained from the series of infants analyzed according to weight. Similar statistics derived according to length of child have been omitted since the totals as well as the incidence of each individual maternal complication were almost identical with the ones shown here. It is of interest to note that on detailed examination of this portion of our material, it was found that the total incidence of maternal complications decreased significantly with increasing weight

and length of the child. Thus a maternal abnormality was found in 46.81 per cent of those infants weighing less than 1500 gm., a figure which fell to 32.89 per cent in the group 2000 gm. and more. Similar analysis revealed percentages of 59.99 and 38.11 with lengths of less than 35 cm. and 40 cm. and more, respectively.

Sex.—Investigators have repeatedly noted that the sex ratio of newborn infants shows a preponderance of males. Thus Crews estimated a conception ratio of 170 males to 100 females, Schultz, 110 to 100 during the abortion stage, and Rauber, 106 to 100 at full term. In view of this, it was surprising to note in this series of infants weighing less than 2500 gm., a reversal of this ratio in both white and black infants, with females outnumbering males 110 to 100, and 107 to 100 for the two races, respectively. Moreover, a similar reversal was found in infants whose length

TABLE VI

THE SEX OF PREMATURELY BORN INFANTS

	PER CENT					
	WHITE		BLACK		TOTAL	
	WEIGHT LESS THAN 2500 GM.	LENGTH LESS THAN 45 CM.	WEIGHT LESS THAN 2500 GM.	LENGTH LESS THAN 45 CM.	WEIGHT LESS THAN 2500 GM.	LENGTH LESS THAN 45 CM.
Males	47.55	46.33	48.35	48.25	48.09	47.65
Females	52.45	53.67	51.65	51.75	51.91	52.35

TABLE VII

SEX RATIOS

	WHITE	BLACK	TOTAL
	MALES TO FEMALES	MALES TO FEMALES	MALES TO FEMALES
Weight less than 2500 gm.	100-110	100-107	100-108
Length less than 45 cm.	100-116	100-107	100-110

at birth was less than 45 cm., with ratios existing of 116 to 100 (white) and 107 to 100 (black). It is our belief, however, that these findings do not indicate a true preponderance of females in prematurely born infants but are to be explained by the normally lower weight and length at birth of this sex, as contrasted with the male. Thus we have found the average birth weight in a series of term infants to be, male and female, respectively: white primiparas, 3270 and 3165 gm.; white multiparas, 3441 and 3313 gm.; black primiparas, 3034 and 2947 gm.; and black multiparas, 3162 and 3027 gm. It would seem plausible to assume that a disproportionate number of females over males are born at full term with weights of less than 2500 gm. and lengths under 45 cm. Further proof of this will be adduced subsequently by the significantly lower stillborn and neonatal mortality rates found for the female infants in the series. In passing, attention is drawn to the unequal ratios found

in white infants analyzed by weight and length (110 to 100 and 116 to 100, respectively) although for the black race identical figures were obtained.

Type of Delivery.—Premature labor which begins accidentally and spontaneously will, in the vast majority of cases, terminate without instrumental or manual aid, breech extraction being the only general exception to this. Other types of operative delivery are occasioned chiefly by some obstetric complication which has necessitated premature termination of the pregnancy or ensue in the desire to immediately deliver a second twin. In other words, we believe that Table VIII reflects

TABLE VIII

INCIDENCE OF CERTAIN OPERATIONS—PER CENT OF TOTAL DELIVERIES

OPERATION	PREMATURE	GENERAL CLINIC POPULATION
Cesarean section	3.45	4.61
Breech extraction	6.78	4.35
Forceps	3.94	13.54
Version	4.35	1.62
Destructive operations	0.67	0.41

the incidence of the causative complications rather than the incidence of various types of delivery deliberately selected as the safest obstetric procedures for the undersized infant. It will be noted that in our series one out of five babies weighing less than 2500 gm. and roughly one out of six less than 45 cm. in length were delivered by operative means. These rates are only slightly below that found for the general clinic population of term infants provided the material is divided according to race of mother as shown in the footnote to Table IX. However, the

TABLE IX

THE OPERATIVE INCIDENCE WITH PREMATURE DELIVERY

	DELIVERY		PER CENT OPERATIVE
	SPONT.	OPER.	
Weight of infant in gm.			
1499 and under	399	119	22.97
1500 to 1999	743	216	22.52
2000 to 2499	1962	442	18.39
Total	3104	777	20.02
Length of infant in cm.			
34 and under	20	11	35.48
35 to 39	309	82	20.97
40 to 44	1584	319	16.76
Total	1913	412	17.72

Operative Incidence: Premature—white 28.09 per cent; black 16.24 per cent. Clinic—white 29.64 per cent; black 19.88 per cent.

type of operation selected to effect delivery of the premature infant as contrasted with the full-term infant varies considerably. Thus, breech extraction and podalic version were necessary more frequently with im-

mature babies, while forceps and cesarean section were employed more often at full term. Attention is drawn to the marked difference in operative incidence for the two races. This is probably explained to a considerable extent by the fact that those maternal complications predisposing to operative delivery (those previously listed with the exception of syphilis) occurred more frequently in white women than in black, 35.03 and 18.96 per cent of total patients, respectively. Finally, it seems significant that the operative rate fell with increasing weight and length of the child, which is graphically illustrated in Table IX.

DISCUSSION

Little discussion seems necessary in addition to that given with each individual analysis. It would, however, seem worthy of emphasis at this point that any attempt at a single standard of prematurity, whether based on weight or length, or both, would result in inaccuracies due to differences according to race, age, parity, and sex. Furthermore, separate criteria would seem necessary in single as contrasted with multiple births. Speculation concerning an accurate weight-length standard, with corrections for the above factors, and particularly with reference to mortality rates, would seem of considerable interest from a practical standpoint as well as contributing to our knowledge of constitution. Such a study, however, to be valuable, should include term as well as premature infants and is not within the province of this article. It is proposed to examine our complete material from the above points of view in the near future.

It is, consequently, our opinion that the figures presented here do not offer a true picture of the incidence of prematurity and that the following rates offer only an indication of the frequency of the birth of infants theoretically viable but below average in weight or length and not necessarily truly premature: less than 2500 gm., 9.19 per cent; and less than 45 cm., 5.55 per cent.

The marked racial differences noted throughout the study are of interest. It would not appear that the increased number of small infants born to colored women is to be explained solely by the fact that this average weight at birth is several ounces below that found for white patients. Syphilis occurred approximately four times as often in the colored as in the white portion of the series, yet this factor also does not afford a complete explanation of the disparity. The negresses making up this clinic population are for the most part second- or third-generation tenement dwellers in a large city. They show evidences generally of physical degeneration, and it seems possible that this might result in an increased number of prematurely born children, as well as a decreased birth weight or length at term. It would be of interest to learn if a similar racial difference would be found in rural areas.

CONCLUSIONS

1. In a large series of consecutively delivered infants, 9.19 per cent weighed less than 2500 gm. at birth, while only 5.55 per cent were under 45 cm. in length. For multiple births similar incidences of 53.00 and 28.11 per cent, respectively, were obtained.

2. The number of second born twins weighing below 2500 gm. was significantly greater than that of first born, indicating a tendency for the heavier child to pass through the birth canal first.

3. Judged by either weight or length the incidence of small infants was almost twice as great in the black as in the white race.

4. Although the obstetrically youthful woman relatively frequently gives birth to a child below the average in size, no definite correlation was determined between maternal age and the true incidence of premature births. A possible exception to this was found in the groups aged 35 years and over where some increase in the number of very small and undoubtedly premature infants was noted.

5. Small infants were born to primiparas more frequently than to any other parous group.

6. No significant increase in the frequency of premature rupture of the membranes was noted in the groups under discussion, as contrasted with a series of deliveries at term.

7. As was to be expected, certain maternal complications, in themselves resulting in premature delivery, either spontaneous or induced, were observed more frequently in this series of cases than in the general clinic population.

8. The sex ratio of the infants comprising this series showed a predominance of females, probably due to the normally smaller birth weight and birth length of the female child.

9. The percentage of premature babies delivered by operative means was essentially that of the general clinic population. Breech extraction and version occurred more frequently and forceps and cesarean section less often in the premature groups.

10. It is our belief that present methods of establishing prematurity on the basis of weight, or length, or both, are grossly inaccurate. Allowances must be made for race, age, and parity of mother, as well as sex of infant. Separate standards are necessary for single and multiple births. Further investigation is necessary to definitely establish these points.

STATISTICAL STUDIES ON PREMATURITY

II. The Mortality of Prematurity and the Effect of Certain Obstetric Factors

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IN A preceding communication a statistical analysis was made on a series of prematurely delivered infants from the point of view of the incidence of early birth and the effect upon the incidence of certain obstetric factors. In the present study it is proposed to reinvestigate the same group of cases in order to derive certain rates of mortality, both stillborn and neonatal, according to varying weights and lengths of the infants at birth. Furthermore, it is desired to ascertain the effects, if any, of such factors as the race, age, and parity of the mother, the type of delivery, etc., upon mortality rates. The series is composed of 4,055 infants weighing less than 2500 gm. at birth and 2,415 measuring less than 45 cm. in length, the two groups comprising 10.29 per cent and 6.13 per cent respectively of 39,394 consecutive viable deliveries occurring on the Obstetrical Service of the Johns Hopkins Hospital.

Gross Mortality Rates.—The general mortality figures obtained from the study are shown in Tables I and I *A* and certain trends are further illustrated in Figs. 1 to 4. Divisions by 100 and 500 gm. and 1 and 5 cm. are noted, together with differences occurring between single and twin births, and white and colored infants. Upon reaching 2500 gm. and 45 cm., mortality rates were found to be still decreasing. Since it was desired to ascertain at what level of weight and length a stationary death rate began, small series of infants between 2500 and 3000 gm. and 45 and 49 cm. were selected at random and the data incorporated into the tables. For the sake of clarity the findings according to weight and length will be discussed separately. For premature infants, recorded in the three brackets under 1200 gm., a falling stillborn rate was compensated for by an increasing neonatal mortality percentage, so that the total mortality remained relatively stationary and at about 90 per cent. From 1200 gm. on there was a steady mortality decrease for each 100 gm. division, becoming relatively rapid in the brackets between 1800 and 2400 gm., then slowing and finally becoming stationary at 2700 gm. and more (Fig. 1). The total mortality fell below 50 per cent in the bracket 1800 to 1900 gm. Deaths per 100 live births also declined steadily above 1200 gm. and became stationary at less than one per cent from 2700 gm. on. This rate fell below 50 per cent between 1600 and 1700 gm. (Fig. 2).

From the Department of Obstetrics, Johns Hopkins University and Hospital.

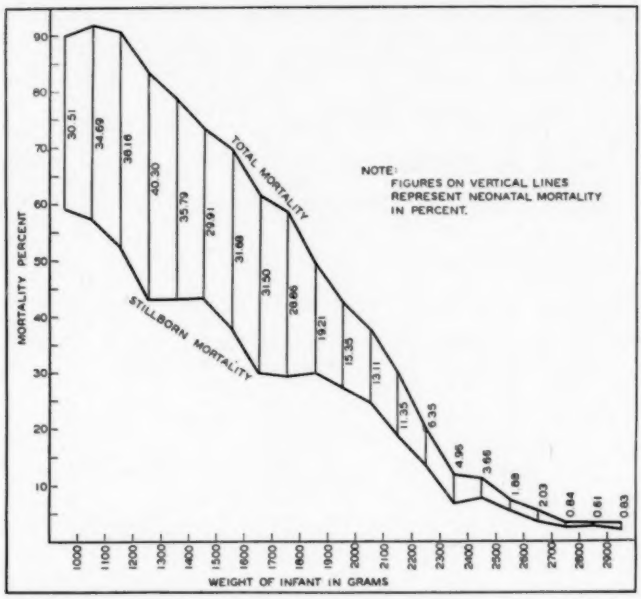

Fig. 1.—Total, neonatal, and stillborn mortality according to weight of infant (single births only).

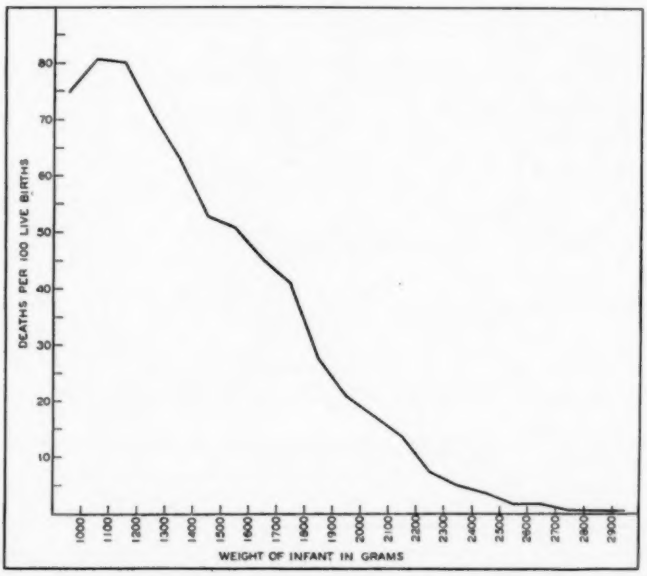

Fig. 2.—Deaths per 100 live births according to weight of infant (single births only).

TABLE I

WEIGHT OF CHILD (GM.)	WHITE								BLACK								BOTH RACES							
	TOTAL BIRTHS	STILLBIRTHS	LIVE BIRTHS	NEONATAL DEATHS	% STILLBORN	% NEONATAL DEATHS	% TOTAL MORTALITY	% NEONATAL DEATHS TO LIVE BIRTHS	TOTAL BIRTHS	STILLBIRTHS	LIVE BIRTHS	NEONATAL DEATHS	% STILLBORN	% NEONATAL DEATHS	% TOTAL MORTALITY	% NEONATAL DEATHS TO LIVE BIRTHS	TOTAL BIRTHS	STILLBIRTHS	LIVE BIRTHS	NEONATAL DEATHS	% STILLBORN	% NEONATAL DEATHS	% TOTAL MORTALITY	% NEONATAL DEATHS TO LIVE BIRTHS
Mortality Rates: Single Births (By 100 Gm.)																								
Less than 1000	26	14	12	11	53.85	42.31	96.16	91.67	33	21	12	7	63.64	21.21	84.85	58.33	59	35	24	18	59.32	30.51	89.83	75.00
1000-1099	15	10	5	3	66.67	20.00	86.67	60.00	34	18	16	14	52.94	41.18	94.12	87.50	49	28	21	17	57.14	34.69	91.83	80.95
1100-1199	25	13	12	10	52.00	40.00	92.00	83.33	51	27	24	19	52.94	37.25	90.19	79.17	76	40	36	29	52.63	38.16	90.79	80.56
1200-1299	18	11	7	6	61.11	33.33	94.44	85.71	49	18	31	21	36.73	42.86	79.59	67.74	67	29	38	27	43.28	40.30	83.58	71.05
1300-1399	25	10	15	10	40.00	40.00	80.00	66.67	70	31	39	24	44.29	34.29	78.58	61.54	95	41	54	34	43.16	35.79	78.95	62.96
1400-1499	39	17	22	15	43.59	38.46	82.05	68.18	78	34	44	20	43.59	25.64	62.23	45.45	117	51	66	35	43.59	29.91	73.50	53.03
1500-1599	48	11	37	23	22.92	47.92	70.84	62.16	113	50	63	28	44.24	24.78	69.02	44.44	161	61	100	51	37.89	31.68	69.57	51.00
1600-1699	50	10	40	16	20.00	32.00	52.00	40.00	77	28	49	24	36.36	31.17	67.53	48.98	127	38	89	40	29.92	31.50	61.42	44.94
1700-1799	61	19	42	19	31.15	31.15	62.30	45.24	88	25	63	24	28.41	27.27	55.68	38.10	149	44	105	43	29.53	28.86	58.39	40.95
1800-1899	69	23	46	14	33.33	20.29	53.62	30.43	160	46	114	30	28.75	18.75	47.50	26.32	229	69	160	44	30.13	19.21	49.34	27.50
1900-1999	53	16	37	7	30.19	13.21	43.40	18.91	149	39	110	24	26.17	16.11	42.28	21.82	202	55	147	31	27.23	15.35	42.58	21.09
2000-2099	96	16	80	13	16.67	13.54	30.21	16.25	232	65	167	30	28.02	12.93	40.95	17.96	328	81	247	43	24.70	13.11	37.81	17.41
2100-2199	112	13	99	12	11.61	10.71	22.32	12.12	214	48	166	25	22.43	11.68	34.11	15.06	326	61	265	37	18.71	11.35	30.06	13.96
2200-2299	144	20	124	10	13.89	6.94	20.83	8.06	344	47	297	21	13.66	6.10	19.76	7.07	488	67	421	31	13.73	6.35	20.08	7.36
2300-2399	148	13	135	13	8.78	8.78	17.56	9.63	356	22	334	12	6.18	3.37	9.55	3.59	504	35	469	25	6.94	4.96	11.90	5.33
2400-2499	191	15	176	10	7.85	5.24	13.09	5.68	410	33	377	12	8.05	2.93	10.98	3.18	601	48	553	22	7.99	3.66	11.65	3.98
2500-2599	165	7	158	6	4.24	3.64	7.88	3.80	366	23	343	4	6.28	1.09	7.37	1.17	531	30	501	10	5.65	1.88	7.53	2.00
2600-2699	203	7	196	5	3.45	2.46	5.91	2.55	389	15	374	7	3.86	1.80	5.66	1.87	592	22	570	12	3.72	2.03	5.75	2.11
2700-2799	277	3	274	1	1.08	0.36	1.44	0.36	557	19	538	6	3.41	1.08	4.49	1.12	834	22	812	7	2.64	0.84	3.48	0.86
2800-2899	346	10	336	3	2.89	0.87	3.76	0.89	630	19	611	3	3.02	0.48	3.50	0.49	976	29	947	6	2.97	0.61	3.58	0.63
2900-2999	442	10	432	4	2.26	0.90	3.16	0.93	760	21	739	6	2.76	0.79	3.55	0.81	1202	31	1171	10	2.58	0.83	3.41	0.85
Mortality Rates: Single Births (By 500 Gm.)																								
Less than 1000	26	14	12	11	53.85	42.31	96.15	91.67	33	21	12	7	63.64	21.21	84.85	58.33	59	35	24	18	59.32	30.51	89.83	75.00
1000-1499	122	61	61	44	50.00	36.07	86.07	72.13	282	128	154	98	45.39	34.75	80.14	63.64	404	189	215	142	46.78	35.15	81.93	66.05
1500-1999	281	79	202	79	28.11	28.11	56.22	39.11	587	188	399	130	32.03	22.15	54.18	32.58	868	267	601	209	30.76	24.08	54.84	34.78
2000-2499	691	77	614	58	11.14	8.39	19.53	9.45	1556	215	1341	100	13.82	6.43	20.25	7.46	2247	292	1955	158	13.00	7.03	20.03	8.08
2500-2999	1433	37	1396	19	2.58	1.33	3.91	1.36	2702	97	2605	26	3.59	0.96	4.55	1.00	4135	134	4001	45	3.24	1.09	4.33	1.12
Mortality Rates: Twin Births (By 500 Gm.)																								
Less than 1000	7	1	6	5	14.29	71.43	85.71	83.33	11	7	4	4	63.64	36.36	100.00	100.00	18	8	10	9	44.44	50.00	94.44	90.00
1000-1499	20	6	14	11	30.00	55.00	85.00	78.57	48	5	43	23	10.42	47.92	58.34	53.49	68	11	57	34	16.18	50.00	66.18	59.65
1500-1999	55	4	51	11	7.27	20.00	27.27	21.57	78	11	67	15	14.10	19.23	33.33	22.39	133	15	118	26	11.28	19.55	30.83	22.03
2000-2499	108	1	107	2	0.93	1.85	2.78	1.87	150	7	143	6	4.67	4.00	8.67	4.20	258	8	250	8	3.10	3.10	6.20	3.20

TABLE I *A*

LENGTH OF CHILD (CM.)	WHITE								BLACK								BOTH RACES							
	TOTAL BIRTHS	STILLBIRTHS	LIVE BIRTHS	NEONATAL DEATHS	% STILLBORN	% NEONATAL DEATHS	% TOTAL MORTALITY	% NEONATAL DEATHS TO LIVE BIRTHS	TOTAL BIRTHS	STILLBIRTHS	LIVE BIRTHS	NEONATAL DEATHS	% STILLBORN	% NEONATAL DEATHS	% TOTAL MORTALITY	% NEONATAL DEATHS TO LIVE BIRTHS	TOTAL BIRTHS	STILLBIRTHS	LIVE BIRTHS	NEONATAL DEATHS	% STILLBORN	% NEONATAL DEATHS	% TOTAL MORTALITY	% NEONATAL DEATHS TO LIVE BIRTHS
Mortality Rates: Single Births (By 1 cm.)																								
Less than 34	12	9	3	1	75.00	8.33	83.33	33.33	13	8	5	3	61.54	23.08	84.62	60.00	25	17	8	4	68.00	16.00	84.00	50.00
35	23	10	13	8	43.48	34.78	78.26	61.54	28	21	7	6	75.00	21.43	96.43	85.71	51	31	20	14	60.78	27.45	88.23	70.00
36	19	9	10	8	47.37	42.11	89.48	80.00	41	25	16	11	60.98	26.83	87.81	68.75	60	34	26	19	56.67	31.67	88.34	73.08
37	25	14	11	9	56.00	36.00	92.00	81.82	48	26	22	15	54.17	31.25	85.42	68.18	73	40	33	24	54.79	32.88	87.67	72.73
38	23	14	9	3	60.87	13.04	73.91	33.33	64	31	33	26	48.44	40.63	89.07	78.79	87	45	42	29	51.72	33.33	85.05	69.05
39	27	11	16	7	40.74	25.93	66.67	43.75	65	22	43	28	33.85	43.08	76.93	65.12	92	33	59	35	35.87	38.04	73.91	59.32
40	54	18	36	21	33.33	38.89	72.22	58.33	127	51	76	31	40.16	24.41	64.57	40.79	181	69	112	52	38.12	28.73	66.85	46.43
41	55	19	36	14	34.55	25.45	60.00	38.89	141	45	96	39	31.91	27.66	59.57	40.63	196	64	132	53	32.65	27.04	59.69	40.15
42	78	15	63	15	19.23	19.23	38.46	23.81	225	64	161	38	28.44	16.89	45.33	23.60	303	79	224	53	26.07	17.49	43.56	23.66
43	131	20	111	30	15.27	22.90	38.17	27.03	281	57	224	34	20.28	12.10	32.38	15.18	412	77	335	64	18.69	15.53	34.22	19.10
44	219	38	181	34	17.35	15.53	32.88	18.78	463	76	387	47	16.41	10.15	26.56	12.14	682	114	568	81	16.72	11.88	28.60	14.26
45	95	8	87	6	8.42	6.32	14.74	6.90	236	15	221	4	6.36	1.69	8.05	1.81	331	23	308	10	6.95	3.02	9.97	3.25
46	204	12	192	2	5.88	0.98	6.86	1.04	419	20	399	12	4.77	2.86	7.64	3.01	623	32	591	14	5.14	2.25	7.39	2.37
47	357	6	351	8	1.68	2.24	3.92	2.28	725	18	707	7	2.48	0.97	3.45	0.99	1082	24	1058	15	2.22	1.39	3.61	1.42
48	601	12	589	7	2.00	1.16	3.16	1.19	1054	36	998	11	3.48	1.06	3.55	1.10	1635	48	1587	18	2.94	1.10	4.04	1.13
49	907	13	894	9	1.43	0.99	2.42	1.01	1417	31	1386	9	2.19	0.64	2.83	0.65	2324	44	2280	18	1.89	0.77	2.66	0.79
Mortality Rates: Single Births (By 5 cm.)																								
Less than 34	12	9	3	1	75.00	8.33	83.33	33.33	13	8	5	3	61.54	23.08	84.62	60.00	25	17	8	4	68.00	16.00	84.00	50.00
35-39	117	58	59	35	49.57	29.91	79.48	59.32	246	125	121	86	50.81	34.96	85.77	71.07	363	183	180	121	50.41	33.33	83.74	67.22
40-44	537	110	427	114	20.48	21.23	41.71	26.70	1237	293	944	189	23.69	15.28	38.97	20.02	1774	403	1371	303	22.72	17.08	39.80	22.10
45-49	2164	51	2113	32	2.36	1.48	3.84	1.51	3831	120	3711	43	3.13	1.12	4.25	1.16	5995	171	5824	75	2.85	1.25	4.10	1.29
Mortality Rates: Twin Births (By 5 cm.)																								
Less than 34	3	0	3	2	0.00	66.67	66.67	66.67	8	4	4	3	50.00	37.50	87.50	75.00	11	4	7	5	36.36	45.45	81.81	71.43
35-39	15	3	12	9	20.00	60.00	80.00	75.00	34	6	28	18	17.65	52.94	70.59	64.29	49	9	40	27	18.37	55.10	73.47	67.50
40-44	68	5	63	15	7.35	22.06	29.41	23.81	125	11	114	18	8.80	14.40	23.20	15.79	193	16	177	33	8.29	17.10	25.39	18.64

In the series analyzed according to length at birth (Table I *A*) the total cases in the lower centimeter brackets were so few as to permit the chance of a considerable sampling error. A steady and relatively consistent fall in stillborn mortality occurred with each added centimeter, an essentially level rate being reached at 47 cm. and above. The total mortality remained fairly constant between 84 and 88 per cent through the length 38 cm., following which a steady fall occurred, this rate also becoming stationary at 47 cm. The total mortality fell below 50 per cent at 42 cm. Deaths per 100 live births declined steadily after 36 cm., the fall becoming very slow from 45 cm. on. This rate fell below 50 per cent at 40 cm.

From the foregoing discussion the following comparative rates may be derived:

1. A steady total mortality was reached at 2700 gm. and 47 cm.

2. The total mortality became less than 50 per cent at 1800 gm. and 42 cm.

3. Deaths per 100 live births fell below 50 per cent at 1600 gm. and 40 cm.

The determination of racial differences in mortality rates was difficult since the probability of sampling errors due to insufficient figures in each individual rubric was great. Generally speaking, stillbirth rates were greater and deaths per 100 live births less in colored infants judged both by weight and length standards. The lower neonatal mortality was particularly evident in the groups 2300 to 2399 and 2400 to 2499 gm., when rates of 9.63 and 5.68 per cent were found for white prematures as contrasted with 3.59 and 3.18 for black. These black percentages correspond roughly with the figure of 3.8 obtained for white babies weighing 2500 to 2599 gm., and it seems probable that the latter weight range in the white race is about the equivalent in maturity to the 2300 to 2400 range level in the black. A finding of considerable interest was the marked difference in death rates for single as contrasted with twin births, as is illustrated in Fig. 4. With the exception of extremely immature infants of less than 1000 gm., the chances of live birth and of survival were much greater for all weights in the twin series, and in the group 2000 gm. and over the ratio was almost three to one. A similar tendency, but by no means as marked, was observed for various lengths. This is taken as confirmation of the closer approach to maturity, at any given weight, of twin infants as contrasted with single born children, whereas the length of the former tends to correspond more closely to the true gestational age.

Attention is drawn at this time to two items illustrated in Tables I and I *A*. Many more infants were found whose weight at birth was under 2500 gm. than whose length was below 45 cm., 3,578 and 2,162, respectively. The stillborn, neonatal, and total mortality rates in the

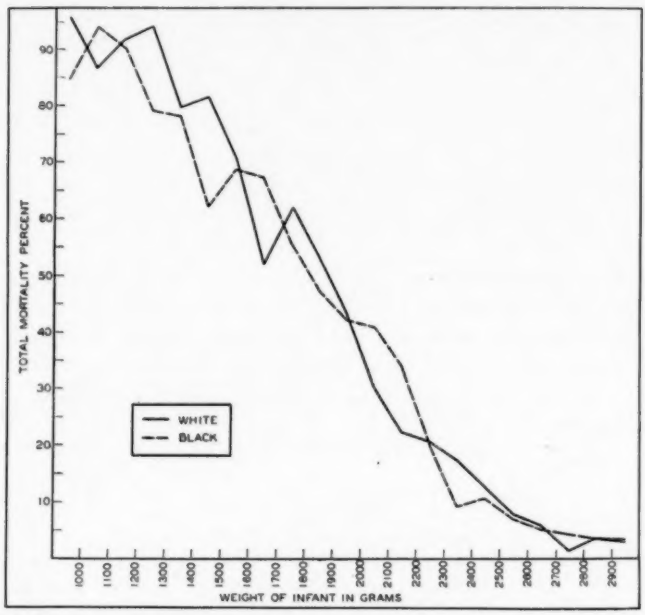

Fig. 3.—Total mortality according to race and weight of infant (single births only).

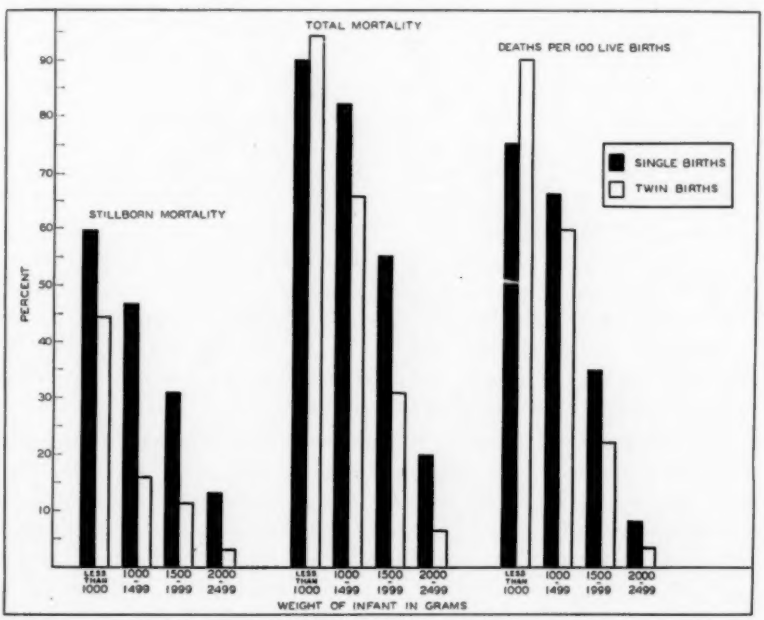

Fig. 4.—Stillborn mortality, total mortality, and deaths per 100 live births according to weight of infant (single versus twin births).

smaller series (length) were considerably higher than in the larger (weight). It is our opinion that these findings indicate the inaccuracy of criteria for prematurity which now link a weight of 2500 gm. and 45 cm. together. If the weight is accepted the length must be increased, and if the length is correct a decrease in the weight criterion must follow. Or, and this has seemed the more logical to us, both of the commonly accepted weight and length standards should be discarded and new ones derived, the accuracy of which would be subject to less criticism.

Mortality Rates: First Versus Second Twin.—In the remaining analyses of this series of prematurly born infants it is planned to group together the single and twin births. First, however, it is desired to present mortality rates for the first born, as contrasted with the second born in twin pregnancies, the prediction having been made that since the former theoretically received the greater trauma during labor (dilatation of cervix, perineum, etc.) its risk should be higher. Table II shows

TABLE II

MORTALITY RATES: FIRST VERSUS SECOND TWIN

WEIGHT	TOTAL BIRTHS	STILL-BIRTHS	LIVE BIRTHS	NEO-NATAL DEATHS	PER CENT STILL-BORN	PER CENT NEONA-TAL DEATHS	PER CENT TOTAL MOR-TALITY	PER CENT NEONATAL DEATHS TO LIVE BIRTHS
First twin:								
1499 and under	39	9	30	22	23.08	56.41	79.49	73.33
1500 to 1999	65	6	59	11	9.23	16.92	25.15	18.64
2000 to 2499	115	2	113	3	1.74	2.61	4.35	2.65
Total	219	17	202	36	7.76	16.44	24.20	17.82
Second twin:								
1499 and under	47	10	37	21	21.28	44.68	65.96	56.76
1500 to 1999	68	9	59	15	13.24	22.06	35.29	25.42
2000 to 2499	143	6	137	5	4.20	3.50	7.69	3.65
Total	258	25	233	41	9.69	15.89	25.58	17.60

the results of this analysis and, although not conclusive, apparently indicates that the risk is about equal for the two infants. Indeed, most of the rates derived according to weight were slightly lower for the first born, but the margin of difference was so small that it could easily be accounted for by a sampling error. On the other hand the chances of the second twin were somewhat better, both for live birth and survival in the series analyzed according to length.

Age.—Table III indicates that whether judged by weight or length at birth, the risk to the prematurely born child increased materially with advancing age of the mother in the series under discussion. This discrepancy would seem to permit explanation in two ways. In the first place, there is both clinical and statistical evidence that the young woman tends to give birth to an infant relatively below average in weight and length. This infant, however, is vigorous and stands a better chance of

survival than a similar one born to an older woman and one more premature in its essential reactions. Secondly, advancing parity accompanies advancing age and it is in these higher parous groups that certain maternal complications, adding materially to the risk of prematurity and infant death, are most commonly found.

TABLE III

MORTALITY RATES ACCORDING TO THE AGE OF THE MOTHER

AGE OF MOTHER	TOTAL BIRTHS	STILL-BIRTHS	LIVE BIRTHS	NEO-NATAL DEATHS	PER CENT STILL-BORN	PER CENT NEO-NATAL DEATHS	PER CENT TOTAL MOR-TALITY	PER CENT NEONATAL DEATHS TO LIVE BIRTHS
			Weight					
19 and under	1272	195	1077	177	15.33	13.92	29.25	16.43
20 to 29	1749	395	1354	253	22.58	14.47	37.05	18.69
30 and over	759	205	554	128	27.01	16.86	43.87	23.10
			Length					
19 and under	781	140	541	144	17.93	18.44	36.37	26.62
20 to 29	1096	309	787	210	28.19	19.16	47.35	26.68
30 and over	490	159	331	104	32.45	21.22	53.67	31.42

Parity.—In view of what has been said regarding age of mothers, rising mortality rates with increasing parity were probably to be expected. The extent to which multiparity adds to the risk of the child is shown in Table IV. The growing stillborn rate was explainable in

TABLE IV

MORTALITY RATES ACCORDING TO THE PARITY OF THE MOTHER

PARA	TOTAL BIRTHS	STILL-BIRTHS	LIVE BIRTHS	NEO-NATAL DEATHS	PER CENT STILL-BORN	PER CENT NEO-NATAL DEATHS	PER CENT TOTAL MOR-TALITY	PER CENT NEONATAL DEATHS TO LIVE BIRTHS
			Weight					
1	1690	270	1420	208	15.98	12.31	28.29	14.65
2 to 4	1315	308	1007	215	23.42	16.35	39.77	21.35
5 and more	780	219	561	137	28.08	17.56	45.64	24.42
			Length					
1	879	196	683	171	22.30	19.45	41.75	25.04
2 to 4	864	242	622	175	28.01	20.25	48.26	28.14
5 and more	534	173	361	116	32.40	21.72	54.12	32.13

terms of the previously mentioned maternal complications. However, the increased number of neonatal deaths in parous women did not lend itself to immediate interpretation. Although not shown in the table it is of interest that both the stillborn rate and that for deaths per 100 live births were twice as great in the group para x and more as in the primiparous division.

Rupture of Membranes.—Table V indicates the mortality rates derived by both weight and length according to the time of rupture of the membranes. Little discussion seems necessary except to note that the lowest rates found were in the group with rupture occurring before the onset of labor. This may be taken as additional evidence that this accident, formerly considered of grave import, is essentially harmless, even to the premature child.

TABLE V

MORTALITY RATES AS AFFECTED BY TIME OF RUPTURE OF MEMBRANES

TIME OF RUPTURE	TOTAL BIRTHS	STILL-BIRTHS	LIVE BIRTHS	NEO-NATAL DEATHS	PER CENT STILL-BORN	PER CENT NEO-NATAL DEATHS	PER CENT TOTAL MOR-TALITY	PER CENT NEONATAL DEATHS TO LIVE BIRTHS
			Weight					
Before onset of labor	582	83	499	77	14.26	13.23	27.49	15.43
First stage	507	121	386	55	23.87	10.85	34.72	14.25
Second stage	1790	365	1425	280	20.39	15.64	36.03	19.65
			Length					
Before onset of labor	309	66	243	64	21.36	20.71	42.07	26.34
First stage	292	80	212	45	27.40	15.41	42.81	21.23
Second stage	1049	271	778	224	25.83	21.35	47.18	28.79

Sex.—In a previous communication attention has been drawn to the interesting finding that the normal preponderance of males at birth was reversed in this series of prematurely born children. In Table VI we

TABLE VI

MORTALITY RATES AS AFFECTED BY THE SEX OF CHILD

RACE AND SEX	TOTAL BIRTHS	STILL-BIRTHS	LIVE BIRTHS	NEO-NATAL DEATHS	PER CENT STILL-BORN	PER CENT NEO-NATAL DEATHS	PER CENT TOTAL MOR-TALITY	PER CENT NEONATAL DEATHS PER 100 LIVE BIRTHS
			Weight less than 2500 gm.					
White, male	620	125	495	124	20.16	20.06	40.16	25.05
White, female	684	116	568	95	16.96	13.89	30.85	16.73
Black, male	1321	327	994	212	24.75	16.05	40.80	21.33
Black, female	1411	248	1163	170	17.58	12.05	29.62	14.62
Total, male	1941	452	1489	336	23.29	17.31	40.60	22.57
Total, female	2095	364	1731	265	17.37	12.65	30.02	15.31
			Length less than 45 cm.					
White, male	347	93	254	97	26.80	27.95	54.75	38.19
White, female	402	92	310	78	22.89	19.40	42.29	25.16
Black, male	799	261	538	174	32.67	21.78	54.45	32.34
Black, female	857	181	676	143	21.12	16.69	37.81	21.15
Total, male	1146	354	792	271	30.89	23.65	54.54	34.22
Total, female	1259	273	986	221	21.68	17.55	39.23	22.41

record the significantly higher mortality rates, both stillborn and neonatal, found throughout in the males as contrasted with the females. It is our opinion that the normally smaller weight and length at birth of the female infant only partly accounts for the observed discrepancy. It is probable that a true sexual difference in ability to survive is presented here.

Effect of Type of Delivery.—In recent years a number of articles have appeared dealing with the effect of the type of delivery upon the mortality rate of prematurely born infants. In order that our figures may be contrasted with those already published by others, Table VII, dealing

TABLE VII

MORTALITY RATES ACCORDING TO TYPE OF DELIVERY

WEIGHT OF CHILD (GM.)	TOTAL BIRTHS	STILL-BIRTHS	LIVE BIRTHS	NEO-NATAL DEATHS	PER CENT STILL-BORN	PER CENT NEO-NATAL DEATHS	PER CENT TOTAL MOR-TALITY	PER CENT NEONATAL DEATHS TO LIVE BIRTHS
			Spontaneous Delivery					
1499 and under	399	178	221	152	44.61	38.10	82.71	68.78
1500 to 1999	743	195	548	169	26.24	22.75	48.99	30.84
2000 to 2499	1962	206	1756	135	10.50	6.89	17.38	7.69
Total	3104	579	2525	456	18.65	14.69	33.33	18.06
			Operative Delivery					
1499 and under	119	58	61	36	48.74	30.25	78.99	59.02
1500 to 1999	216	81	135	57	37.50	26.39	63.89	42.22
2000 to 2499	442	86	356	27	19.46	6.11	25.57	7.58
Total	777	225	552	120	28.96	15.44	44.40	21.74
			Cesarean Section					
1499 and under	22	9	13	11	40.91	50.00	90.91	84.62
1500 to 1999	31	9	22	7	29.03	22.58	51.61	31.82
2000 to 2499	81	12	69	9	14.81	11.11	25.92	13.04
Total	134	30	104	27	22.39	20.15	42.54	25.96
			Breech Extraction					
1499 and under	38	18	20	7	47.37	18.42	65.79	35.00
1500 to 1999	88	24	64	29	27.27	32.95	60.22	45.31
2000 to 2499	137	20	117	5	14.60	3.65	18.25	4.27
Total	263	62	201	41	23.57	15.59	39.16	20.40
			Forceps					
1499 and under	13	2	11	5	15.38	38.46	53.84	45.45
1500 to 1999	17	3	14	3	17.65	17.65	35.30	21.43
2000 to 2499	123	14	109	5	11.38	4.07	15.45	4.59
Total	153	19	134	13	12.42	8.50	20.92	9.70
			Version and Extraction					
1499 and under	28	12	16	13	42.86	46.43	89.29	81.25
1500 to 1999	58	30	28	15	51.72	25.86	77.58	53.57
2000 to 2499	83	30	53	5	36.14	6.02	42.16	9.43
Total	169	72	97	33	42.60	19.53	62.13	34.02

TABLE VIII

MORTALITY RATES

STILLBIRTHS, NEONATAL DEATHS, AND DEATHS DURING FIRST YEAR

WEIGHT	WHITE				BLACK				TOTAL			
	PER CENT STILL-BORN	PER CENT NEONATAL DEATHS	PER CENT DIED FIRST YEAR	TOTAL	PER CENT STILL-BORN	PER CENT NEONATAL DEATHS	PER CENT DIED FIRST YEAR	TOTAL	PER CENT STILL-BORN	PER CENT NEONATAL DEATHS	PER CENT DIED FIRST YEAR	TOTAL
1499 and under	46.86	40.57	4.00	91.43	43.05	35.29	8.56	86.90	44.26	36.98	7.29	88.53
1500 to 1999	24.70	26.79	9.52	61.01	29.92	21.80	13.38	65.10	28.17	23.48	11.99	63.64
2000 to 2499	9.76	7.51	8.26	25.53	13.01	6.21	10.14	29.36	11.98	6.63	9.66	28.27
G. C. P.*	4.43	2.60	3.76	10.79	6.47	3.08	5.09	14.64	5.75	2.91	4.61	13.27

*General clinic population.

with this item, is included. It is not our belief that this table shows in any way the comparative risk rate to the infant according to the method of delivery, per se. In the vast majority of those cases delivered by operative means, breech extraction alone excluded, the choice was dictated by some maternal complication such as heart disease or placenta previa rather than through conscientious effort to produce a living infant. Consequently, the rates appearing in Table VII would seem to reflect the mortality from the maternal abnormality rather than that associated with any given type of delivery. Mortality rates according to type of delivery but derived according to length of child were so similar to those shown here that they have not been included in the table.

Mortality During the First Year of Life.—A relatively large number of the mothers of the infants under analysis returned to the dispensary for examination one year after delivery, and at this time information was obtained concerning the course during the first year of those children discharged alive. This mortality during this period, coupled with the stillborn and neonatal rates, is shown in Table VIII, which further includes similar figures obtained from the general clinic population on children normal in weight at birth. No similar figures are available according to length. It has been the policy of the clinic to discharge the small baby from the hospital only when it has attained a minimum weight of 5½ pounds, presents no abnormality, and is gaining satisfactorily. Despite apparent normality at this time, the death rate of these infants during the first year of life was high, and even in the theoretically most hardy group, with a birth weight between 2000 and 2499 gm., was 8.26 and 10.14 per cent for the white and colored races, respectively. As contrasted with a normal series of term infants, stillbirths, neonatal deaths, and deaths during the first year of life occurred at least twice as often in both black and white children weighing between 4.4 and 5.5 pounds at birth.

DISCUSSION

In the foregoing paragraphs data have been presented on two series of infants below average in weight or length at birth. Little discussion seems necessary in addition to that noted under each individual topic. The purpose of this article has been to present facts obtained from statistical data. Accordingly no positive statements on the prevention of premature birth seem warranted or desirable. Moreover, the care of the prematurely liveborn infant is deemed a problem for the pediatrician rather than the obstetrician. It is of interest to note, however, that the babies making up this series have been born over a period of the past forty years and have been cared for under the rapidly changing regimes of that time. Despite radical alterations in care and feeding, attempts

on our part to adduce changes developing in neonatal mortality rates from decade to decade have not met with any significant findings.

A number of articles have appeared recently dealing with the effect of the type of delivery and anesthetic upon the prematurely born infant. We are unable to agree with the rather optimistic findings of some of these. A relatively high stillborn mortality rate seems unavoidable, since the premature labor and birth so often is the result of fetal death in utero, which in turn has been caused by some maternal complication such as nephritis or syphilis. Furthermore, the premature baby, although born alive, often succumbs in the first few hours of life as the result, apparently, of prolonged partial asphyxia from such conditions as placenta previa or premature separation of the placenta. It would seem that when the early birth is due to maternal complications, high mortality rates are unavoidable and that only when the premature labor is apparently accidental may reasonably low results be expected. Obviously the immature fetus cannot withstand the stresses and strains of labor and delivery with such impunity as does the term one. Consequently, whatever course will subject it to the least number of uterine contractions during labor, and the least trauma at birth, would seem to offer the best results. Each case must then be individualized, and as a guide one can only suggest conservatism. Forceps, version, etc., may occasionally be warranted because of maternal conditions, but should rarely be indicated by the prematurity of the infant. Furthermore, it is well to remember that even cesarean section does not guarantee a live baby and that stillbirths and neonatal deaths will occasionally follow this procedure. Finally, it seems evident that anesthesia and analgesia are to be avoided in this type of case in so far as is possible and that the former, when necessary, be of the saturation rather than the asphyxiation type.

CONCLUSIONS

1. In two large series of premature infants, decreasing stillborn and neonatal mortality rates were noted with increasing weight and length. This decrease was slow in the lower weight brackets (under 1200 gm.), became particularly rapid with weights between 1800 and 2400 gm., and reached a relatively stationary low level at 2700 gm. With increasing length the fall was steady, and a level rate was reached at 47 cm.

2. In general, stillborn rates were higher and deaths per 100 live births lower in black than in white infants.

3. Stillborn and neonatal rates were definitely lower in multiple than in single births. No significant difference was noted in the mortalities of first versus second twins.

4. Judged by either weight or length standards mortality rates increased significantly with advancing age of the mother.

5. A rising mortality was observed with increasing parity of the mother and was twice as great in the group para x and more as in the primiparous portion of the series.

6. No significant effect on mortality was found according to time of rupture of membranes.

7. A much higher stillborn and neonatal death rate was noted in male as contrasted with female infants.

8. An analysis of mortality rates according to type of delivery permitted no definite statement as to the most favorable procedure for the immature infant.

9. A high mortality during the first year was found in those premature infants who survived the first weeks of life.

THE INFLUENCE OF METABOLISM ON TEETH

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THE medical profession no less than the dental profession has reason to be interested in the welfare of the human dentition, and signs are not lacking that this interest is becoming articulate, as indicated by the appearance in medical journals of articles dealing with teeth and the causes and prevention of dental caries. Under the circumstances we feel that it may be appropriate to present briefly various causal factors influencing the caries syndrome in the light of newer data.

Miller[1] in 1883 focussed the attention of the dental profession on local causes of dental caries by his demonstration that this process is inaugurated by chemicoparasitic activity in carbohydrate material retained on the tooth surface either in crevices or on areas not readily cleansed by food scouring or other methods. Miller's theory failed to explain completely all clinical facts, hence there has been a more or less continuous search through the intervening years for an explanation of discrepancies as well as a means for control of the carious process itself.

Recently conviction has been gaining strength that metabolic factors have much to do with the etiology and also the control of dental caries. These may influence the incidence of caries in one of two ways: (1) the tooth structure may be defective (shown chiefly as enamel hypoplasia) because of abnormal metabolism during the period of tooth formation, making it susceptible to what may be called amelolytic influences; (2) current metabolic influences expressing themselves (a) as functions of the saliva, which controls largely the environment of the tooth, and (b) possibly through nutrient channels (as yet little understood) within the tooth. Most recent researches in dental caries tend to be directed toward the solution of the problem by means of efforts to influence metabolism in one or the other of the senses just stated by regulation of the diet and other physiologic factors.

ENAMEL HYPOPLASIA

There are several important differences between formative enamel defects (hypoplastic enamel) of the deciduous and permanent teeth. In the deciduous dentition the crowns are fully formed and very largely calcified in utero, hence hypoplastic enamel in these teeth is chargeable to prenatal systemic disturbance. The hypoplastic deciduous tooth is smooth when erupted but lacks density. Jones[2] has stated that in severe

From The Murry and Leonie Guggenheim Dental Clinic, New York.

hypoplasia the enamel may be soft and chalky at the time of tooth eruption. Caries attacks large areas of the hypoplastic deciduous tooth which may decay with rapid loss of enamel en masse (Figs. 1 and 2).

In the permanent dentition, crown formation and calcification of even the first teeth to erupt, the central incisors and first molars, begins at about the time of birth, hence hypoplasia of enamel is traced to

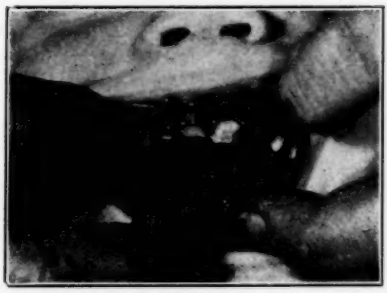

Fig. 1.—Photograph of girl, 21 months of age, showing extensive decay due to deficient enamel formation. The mother's diet during the pregnancy was extremely deficient in calcium and vitamins.

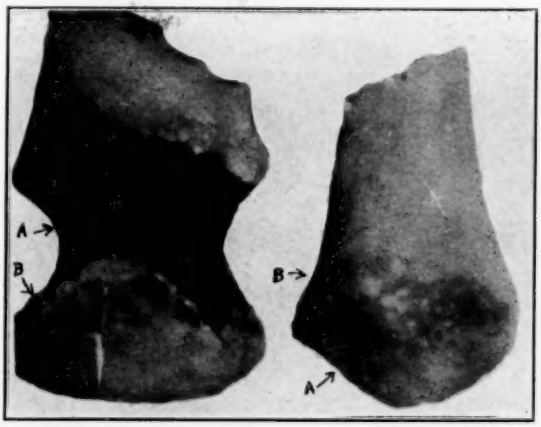

Fig. 2.—Photomicrograph (×6) of upper central and lateral incisor from the same mouth. Caries has attacked areas *A,A* of hypoplastic enamel but has not attacked areas *B,B* where enamel was well formed and well calcified. The crowns of the deciduous teeth are formed in utero, hence the enamel defect and subsequent decay are chargeable to prenatal conditions. What apparently occurred was an illness causing deranged metabolism at the time when areas *A,A* were being formed, preceded and followed by good health with normal metabolic status as evidenced by the good enamel found at *B,B*. (The central incisor [left] begins to form before the lateral incisor.)

systemic disturbance at and following birth. Hypoplastic enamel is pitted and may present grooves, but calcification of the deformed structure is usually normal in its density. It is not prone to decay unless the grooves and pits are of such a depth as to make self-cleansing and cleansing by the tooth brush difficult (Figs. 3 and 4).

In this connection it should be mentioned that Mellanby[3] has claimed that enamel structure is the chief factor in caries resistance and that hypoplastic enamel is likely to decay because of inferior resistance. Clinical evidence does not corroborate this view as regards the permanent teeth, and it seems more likely, in view of other evidence, to be mentioned later, that the same metabolic influences that caused the enamel hypoplasia produce also influences favoring dental caries. However, decay may occur in enamel through environmental or metabolic influences, no matter how perfectly it is formed and calcified.

Fig. 3.

Fig. 4.

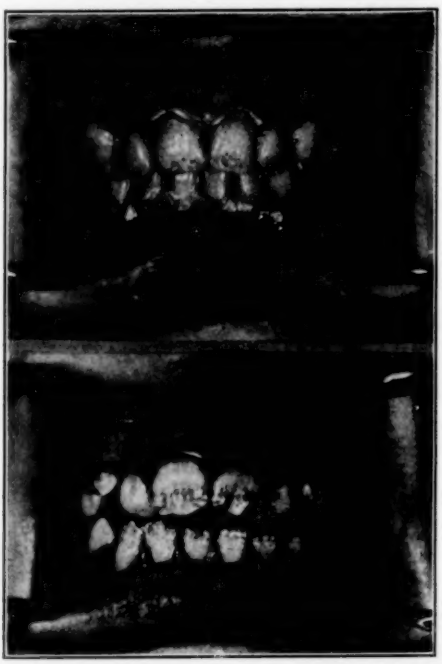

Fig. 3.—Photograph of teeth of boy, aged 10 years, showing mild enamel hypoplasia of the upper central incisors. These teeth usually are not susceptible to caries.

Fig. 4.—Photograph of teeth of girl, aged 10 years, showing marked enamel hypoplasia of all incisors and cuspids. Because of the depth of some of the pits, decay will occur unless protective fillings are placed.

PREGNANCY AND DENTAL CARIES

Tooth structure in relation to caries has received attention from a different viewpoint, viz., the influence of pregnancy on caries. There has been a rather general assumption (1) that women are more susceptible to caries during pregnancy than at other times, and (2) that this assumed special susceptibility is due to withdrawal of calcium salts from the teeth to meet fetal needs. This would imply that tooth structure could be altered after eruption.

Schour[4] has recently presented certain phases of the pathology of the dental tissues, also evidence that teeth are not a storehouse for calcium. He then infers that pregnancy does not influence caries. Review of other evidence seems to indicate that this viewpoint is not conclusive. He derives support for this hypothesis largely from a research by Ziskin,[5] which consists of observations made primarily from the dental standpoint. Because of inherent difficulty in an investigation of this type, little evidence was brought forward as to the metabolic status of the women examined. Indications of this might be obtained by one of several methods. Jay, Hadley, and Bunting[6] have shown a relationship between presence or absence of *Lactobacillus acidophilus* in the mouth and caries immunity or susceptibility. Fosdick and Hatton[7] have announced a test, based on solution of tooth shavings by the saliva as a criterion of caries immunity or susceptibility. Krasnow, Oblatt, and Hirschfeld,[8] through salivary analysis, have suggested a double correlation between certain elements in the saliva and tendency to caries and other dental disease. Still others might be enumerated.

The metabolic state would have to be determined by some reliable method in a study of caries in pregnancy, since it could easily happen that many of the nonpregnant women examined would be caries susceptible and the pregnant women nonsusceptible. Also, pregnant women, except in the lowest economic strata, have prenatal care involving not only diet recommendation, but also instructions tending to bring the physiologic plane to the optimum level. Even in earlier generations, metabolism (hence tooth metabolism) during pregnancy might have been better because of the belief that the expectant mother should have sufficient rest and should eat for two. This would tend to provide good caries resistance in the average case.

GENERAL HEALTH: DENTAL HEALTH

Until more evidence is forthcoming it is safer to assume that dental health is no less a resultant of those conditions which make for the health and life of the body as a whole than that it is itself one of these factors. The teeth have their specific function and in all probability are associated with specific metabolisms. Dental disease, caries, erosion, etc., therefore, may be interpreted as the effect of specific syndromes.

Jones,[9] from her work with dogs at the University of California as well as with children in Honolulu, concludes a relationship between food and teeth. Similar interdependence is implied by Hawkins.[10] Boyd, Drain, and Stearns[11] hypothesize a close correlation between metabolic efficiency and resistance of the tooth to decay. In order to reduce substantially the incidence of dental disease, especially in temperate zones, Mellanby[12] believes that it is necessary to introduce large changes in the diet and habits of pregnant and lactating women, of

TABLE I

ANALYSES ON TOTAL UNSTIMULATED SALIVA[8]

SUMMARY OF RESULTS OBTAINED BY THREE COMMON STATISTICAL METHODS FOR EVALUATING PROBABLE SIGNIFICANCE OF FIGURES

ANALYSES	EROSION*									CARIES†								
	AVERAGE RANGE NOT OVERLAPPING NORMAL‡			DISTRIBUTION MORE THAN 50% ABOVE AVERAGE NORMAL RANGE			ODDS AGAINST RANDOM DEVIATIONS[6]			AVERAGE RANGE NOT OVERLAPPING NORMAL‡			DISTRIBUTION MORE THAN 50% ABOVE AVERAGE NORMAL RANGE			ODDS AGAINST RANDOM DEVIATIONS[6]		
	TOTAL	ALK.	ACID	TOTAL	ALK.	ACID	TOTAL	ALK.	ACID	TOTAL	ALK.	ACID	TOTAL	ALK.	ACID	TOTAL	ALK.	ACID
H^+, pH	6.83 ±0.05	7.19 ±0.07	6.73 ±0.04	89	–	–	1341.0	1.0	15×10^6	6.92 ±0.06	7.21 ±0.04	6.71 ±0.04	62	–	–	26.4	1.9	4×10^5
Calcium	7.6 ±0.5	5.5 ±0.5	8.2 ±0.5	74	25	87	6.3	1.6	13.6	6.2 ±0.2	6.0 ±0.25	6.4 ±0.19	22	11	33	–	1.0	–
Magnesium	0.75 ±0.10	0.41 ±0.04	0.84 ±0.12	68	0	87	8.5	1.0	13.6	0.65 ±0.06	0.63 ±0.06	0.73 ±0.08	65	67	75	5.4	2.2	9.9
Inorganic phosphate	18.0 ±1.4	12.2 ±1.6	19.7 ±1.5	53	25	60	2.6	2.6	9.9	14.4 ±0.6	12.6 ±0.7	15.2 ±0.7	39	11	50	1.0	6.3	–
Protein	446.0 ±46.0	284.0 ±33.0	489.0 ±53.0	68	25	80	22.2	–	44.8	346.0 ±24.0	315.0 ±33.0	359.0 ±39.0	54	33	67	3.0	1.0	2.2
Lipid phosphorus	0.52 ±0.11	0.26 ±0.11	0.60 ±0.14	78	50	86	37.4	1.4	44.8	0.20 ±0.03	0.19 ±0.02	0.22 ±0.04	63	78	50	7.3	4.6	3.5
Cholesterol	11.2 ±2.0	5.3 ±2.1	12.9 ±2.5	57	25	65	3.5	1.0	7.3	10.7 ±0.77	9.2 ±0.7	11.9 ±1.2	82	67	92	31.4	3.0	26.4

*Erosion refers to subjects suffering from wastings: erosions or abrasions.

†Caries refers to subjects with active decay processes only.

‡Normal values obtained from analyses on subjects who as far as medicodental clinical and laboratory tests could discern had no ailments. Hydrogen-ion concentration: 7.14±.04; calcium: 6.3±.4; magnesium: 0.46±.07; inorganic phosphate: 15.2±1; protein: 298±17; lipid phosphorus: 0.13±.02; cholesterol: 7.5±.7.

infants, and of children during the whole period of dental development, and, indeed, during the whole lifetime.

RECENT DATA ON SALIVA

Researches by Krasnow et al.[8] on the quantitative salivary analysis of individuals suffering from caries or erosion and also of those who are caries-free indicate characteristically different chemical pictures of saliva for different dental conditions. Table I summarizes some recent data. From this it will be seen that in erosion the average range of hydrogen-ion concentration, calcium, magnesium, inorganic phosphate, protein, lipid phosphorus, and cholesterol lies entirely beyond that for the same constituents in saliva of normal individuals. The standard deviations are relatively small, and none of the average ranges overlap, hence variations from the normal are probably significant. In caries-active individuals variations from the normal are fewer, nonoverlapping figures appearing only for hydrogen-ion concentration, magnesium, lipid phosphorus, and cholesterol.

It seems plausible to assume a common mechanism at work. The results imply a tendency to that type of derangement often associated with acidic states in the body,[13] notwithstanding that the subjects, for the most part, had no other pathologic involvement as far as the usual medicodental clinical and laboratory tests could discern. Detailed perusal of accumulated data, coordinated with the fact that the organism makes every effort to rid itself of acid ions in salt form, led to the examination of the dietary acid-base potentialities in addition to the usual orthodox factors.[9, 10]

In the plan adopted[14, 15] the chief criteria of physiologic response are subjective guides, clinical manifestations (roentgenograms), weight changes, and variation in the chemical composition of saliva. To insure saliva samples which are duplicable and representative of an individual, conditions are set for a definite metabolic plane over a period of at least one week preceding any analyses.

The variations noted in the saliva in different oral conditions, especially as regards the number of constituents in which variations are found, furnish the basis for the view indicated earlier, that the teeth are associated not with calcium metabolism alone, but with several specific metabolisms upon which general metabolism depends, and that dental health is closely related to the health and life of the body as a whole. It is interesting and perhaps significant that aberrant salivary values can be brought within the normal range by nutritional regulation (Table II). Furthermore, clinical evidence is accumulating which points to the lessening of susceptibility to erosion and caries under such a regime. Indications are that while calcium values in the saliva may not, under certain conditions, vary markedly from the normal, other constituents do, and calcium intake should receive consideration along

TABLE II[14]

CASE REPORT

Patient 16 C, 15 years old, healthy, from excellent home of good economic status.

DEC. 6, 1935	APRIL 1, 1936	OCT. 10, 1936
I. Findings:	I. Findings:	I. Findings:
A. Saliva	*A. Saliva*	
pH 7.1	pH 7.0	
Calcium mg % 5.3	Calcium mg % 5.0	
Phosphorus mg % 13.2 Tending low	Phosphorus mg % 15.5 Increased	
Magnesium mg % 0.62 High	Magnesium mg % 0.41 Decreased	
Protein mg % 300	Protein mg % 306	
Cholesterol mg % 10.9 High	Cholesterol mg % 6.5 Decreased	
Lecithin mg % 0.18 Tending high	Lecithin mg % 0.14 Decreased	
B. Diet	*B. Diet*	
Water, milk low.	Milk increased, water low.	
Calories somewhat low.	Calories increased.	
Acid:base 61:45.	Acid:base 41:55.	
High bread, cake, cereal.	Decrease in bread, cereal.	
C. Dental Report	*C. Dental Report*	*C. Dental Report*
Caries extremely rampant occlusally and interproximally.	Apparently no noticeable change.	Interproximal decalcification arrested. No new cavities. Enamel texture improved.
II. Recommendations:	II. Recommendations:	II. Recommendations:
Increase milk to 3 glasses.	Increase water intake.	Continue with previous advice.
Slowly increase water to 8 glasses.	Use pablum instead of other cereal.	
Slowly increase vegetables } especially	Substitute fruit for cake dessert.	
Slowly increase fruits } raw	Use irradiated milk instead of cod-liver oil.	
Take 2 teaspoonfuls cod-liver oil.		
Decrease slowly bread, cake, etc.		
Keep caloric intake at 1,800.		

with other factors in dietary correction. It should apparently be, and can well be, gained from natural food sources.

We hope that with the presentation of this evidence the medical profession will defer acceptance of theories founded on limited investigation, pending the inauguration of a much needed and really comprehensive research.

CONCLUSIONS

Hypoplastic enamel of the permanent teeth is no more subject to caries than normal enamel unless structural defects are severe. In the deciduous teeth hypoplastic enamel is much more susceptible to caries than normal enamel; a governing factor in the incidence of caries in these teeth seems to be environmental influence, which is, in its turn, apparently related to the metabolic status of the body.

Calcium may not be withdrawn from the teeth through the blood stream during pregnancy, but there exists the possibility that the caries process may be accelerated as a result of unfavorable metabolic conditions, which in turn may also result in unfavorable environmental conditions.

Calcium therapy per se (administration of calcium salts) has not been proved to be beneficial to the teeth. At the same time adequate intake of calcium-containing foods cannot be overlooked in its relationship to normal tooth formation.

Stress laid on one need must always be coordinated with all other physiologic needs directly or indirectly associated with the situation at hand.

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THE BIOPHOTOMETER AS A TEST FOR VITAMIN A DEFICIENCY

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METHODS for the detection of subclinical avitaminosis are being sought for all the vitamins. Considerable investigation has been carried out with regard to vitamin A.

One of the conditions resulting from vitamin A deficiency is night blindness. It is caused by a failure in the regeneration of visual purple after a bleaching by strong light. Administration of cod-liver oil, butter, or milk results in improvement by the third to fifth day, and vision becomes practically normal by the seventh to fourteenth day. Night blindness may be caused by other conditions than vitamin A deficiency.

Using the fact that night blindness is caused by lack of vitamin A, Jeans and Zentmire,[2, 3] with a Birch-Hirschfeld photometer, studied the dark adaptation of a group of children. As a result of this study they found that 26 per cent of the children from rural districts, 53 per cent of children from villages, and no less than 56 to 79 per cent of urban children showed decreased dark adaptations. In a group of eighty-seven children with decreased dark adaptation, eighty-four or 95 per cent returned to normal with the administration of vitamin A. Similar results have been reported by others. Using the same type of instrument and technique, we were unable to obtain satisfactory and consistent results.[5] We concluded, "In our hands the Birch-Hirschfeld photometer was unsatisfactory for the estimation of small variations in dark adaptation such as might be produced by vitamin A deficiency."

Subsequently, Jeans et al.[6] in a later report stated, "This instrument (Birch-Hirschfeld) is not adapted for the satisfactory use in the manner employed," and they described a new instrument devised for this particular test called the biophotometer. Using the latter instrument on a group of thirty-seven children, they obtained results which indicated that 19 per cent were suffering from vitamin A deficiency.

Jeghers,[7] with a group of adults, reports that vitamin A deficiency was common and could be photometrically detected. In a group of medical students 35 per cent were low, and 12 per cent had clinical manifestations of the deficiency. There was complete recovery in three days after an experimentally produced vitamin A deficiency.

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Read at the Tenth Annual Meeting of the Society for Pediatric Research, Great Barrington, Mass., May 4, 1938, and at the Sixteenth Annual Meeting of the Canadian Society for the Study of Diseases of Children, Kingston, Ont., June 3 and 4, 1938.

Palmer and Blumberg[8] recently have reported that "the biophotometer test does not appear to constitute an accurate or reliable technique for detecting mild degrees of vitamin A deficiency in the routine survey of school children." Palmer[9] further reported an investigation of the effect of vitamin A administration on the biophotometer dark adaptation measurements in school children. He states "The results showed no significant difference in the improvement in biophotometer measurements between a group of children whose diet was supplemented and a control group whose diet was not supplemented with vitamin A."

These reports were of extreme interest to us. We have subsequently obtained a biophotometer* as described by Jeans et al. and have made tests according to the technique and standards given in their report.

PROCEDURE

A group of average Toronto school children were tested on repeated occasions during the past year. They were tested on Saturday mornings so as to not interfere with school attendance. They came from all parts of the city with no special selection. The first test was made and it was repeated within three weeks, with no addition to the diet. The children were then given 13,000 units of 50 per cent oleum percomorphum† daily for three weeks, and then a third test was done. The oil was continued for a second three-week period, and a fourth test was made. As far as could be ascertained the children all took the oil.

RESULTS

Table I shows the comparison of the dark adaptation in the first test with the second test. Theoretically these two tests should show a marked degree of correlation as there was no change in the feeding routine in

TABLE I

A COMPARISON OF DARK ADAPTATION AS SHOWN BY THE FIRST TEST WITH THE SECOND TEST: NO CHANGE IN VITAMIN A INGESTION

	FIRST TEST	SECOND TEST		
		UNCHANGED	IMPROVED	DECREASED
Abnormal	17	11	6	–
Borderline	14	5	3	6
Normal	3	2	–	1
Total	34	18	9	7

the interval. Of 34 children, 18 gave readings in the same range on the second test, and 16 were different. Of those that changed, 9 improved and 7 decreased in dark adaptation.

Table II shows the comparison in 34 subjects of the dark adaptation in the second test which was made prior to the administration of vitamin A, with the third test made after three weeks of administration of

*Frober-Faybor Company.

†Kindly supplied by Mead Johnson & Company.

at least 13,000 international units of vitamin A. Theoretically one would expect the abnormal and borderline subjects to improve. Eight of 17 abnormal subjects and 3 of 8 borderline improved; one borderline decreased, and no less than 4 of 9 normal range subjects became borderline or abnormal.

TABLE II

A COMPARISON OF DARK ADAPTATION AS SHOWN BY THE SECOND TEST WITH THE THIRD TEST, MADE AFTER THREE WEEKS OF DAILY INGESTION OF VITAMIN A*

	SECOND TEST	THIRD TEST		
		UNCHANGED	IMPROVED	DECREASED
Abnormal	17	9	8	–
Borderline	8	4	3	1
Normal	9	5	–	4
Total	34	18	11	5

*At least 13,000 international units were used.

Table III shows the comparison in 24 subjects between the third test which was made after three weeks of vitamin A administration with the fourth test after six weeks of vitamin A administration. Three of

TABLE III

A COMPARISON OF DARK ADAPTATION AS SHOWN BY THE THIRD TEST, MADE AFTER THREE WEEKS OF INGESTION OF ADDITIONAL VITAMIN A, WITH THE FOURTH TEST, MADE AFTER INGESTION OF ADDITIONAL VITAMIN A FOR SIX WEEKS

	THIRD TEST	FOURTH TEST		
		UNCHANGED	IMPROVED	DECREASED
Abnormal	10	7	3	–
Borderline	6	3	–	3
Normal	8	5	–	3
Total	24	15	3	6

10 abnormal subjects improved and none of 6 borderline improved; 3 of 6 borderline subjects decreased, and 3 of 8 normal became borderline or abnormal subjects.

Table IV shows the comparison in 24 subjects between the second test and the fourth test, or before and after six weeks of vitamin A administration, during which time 13,000 international units of vitamin A were administered daily. Three of 13 abnormal subjects and 2 of 6 borderline improved; 1 borderline and 2 of 5 normal range subjects decreased.

TABLE IV

A COMPARISON OF DARK ADAPTATION OF THE SECOND TEST, MADE PRIOR TO ADMINISTRATION OF ADDITIONAL VITAMIN A, WITH THE FOURTH TEST, MADE AFTER A PERIOD OF SIX WEEKS*

	SECOND TEST	FOURTH TEST		
		UNCHANGED	IMPROVED	DECREASED
Abnormal	13	10	3	–
Borderline	6	3	2	1
Normal	5	3	–	2
Total	24	16	5	3

*Thirteen thousand units of vitamin A were administered daily during this period.

DISCUSSION

The results shown above are variable and have very little consistency. Hecht et al.,[10] in investigating dark adaptation, have shown that certain factors play a part which may explain the inconsistencies observed with the use of the Birch-Hirschfeld instrument and biophotometer. They pointed out that dark adaptation to ordinary bright light was a factor of both rods and cones. The cones adapted very rapidly, approximately ten times as fast as the rods, and had completely recovered in three to five minutes. Adaptation to red light was mainly by the cones. Adaptation to violet light corresponded to the usual cone adaptation seen with ordinary bright light, after which it followed the curve of rod adaptation, but the subject stated that the light appeared colorless during this latter period. These observers showed that the time of complete cone adaptation and appearance of rod adaptation varied with normal individuals to quite a large degree, but the shape of the curves was similar. They found that the shape of curve for adaptation could not be drawn from the average of a number of individuals because this flattened out the dividing portion between cone and rod adaptation. They also found a rapid and a delayed type of rod adaptation. The former was thought to be due to regeneration of the visual purple that had been changed by exposure to bright light, and the latter, due to a new formation from fresh substances in retina and blood stream; this formation is only called into play when there is extreme destruction of visual purple following exposure to very bright light. In the method used by these observers the test light entered the eye from an angle, and also it was intermittent. This would be difficult to manage with young children. Obviously from the report of the above authors the measurement of dark adaptation is a complicated process and requires a much more difficult technique than is at present used with the biophotometer.

CONCLUSIONS

We have found the biophotometer unsatisfactory as a method of estimation in children of the variations in dark adaptation such as might be produced by vitamin A deficiency.

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THE NEW TUBERCULIN PATCH TEST

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THE object of this paper is to discuss the tuberculin patch test recently described by Vollmer and Goldberger,* and to point out its ease of application and its reliability. Although previous attempts have been made to produce a successful patch or plaster test for tuberculosis, none have been satisfactory. It is not within the scope of this paper to discuss these reasons, nor to discuss the history of the tuberculin test in its various forms.

At the Pine Breeze Sanatorium patch tests† were run on ninety-one tuberculous children in the institution, and on five normal adults. In all but two instances, coincidental Mantoux tests (dilution 1:1000 O. T.‡) were performed. On these two patients recent Mantoux tests had been strongly positive.

Fig. 1.—Mantoux test and patch test.

Half of the patch tests were prepared from old beef extract medium, and the remaining half were prepared with the use of a synthetic medium made after Siebert's formula. No discrimination was made between the two types. They were applied in rotation—first one, then the other, etc.

The results of this series show the reliability of the patch test as compared with the Mantoux test. Ninety (93.75 per cent) of the persons

Table I

	Cases	Percentage
Conformity between Mantoux and patch tests	90	93.75%
Positive patch test—negative Mantoux test	6	6.25%
Negative patch test—positive Mantoux test	0	0%

*Vollmer, H., and Goldberger, E. W.: Am. J. Dis. Child. 54: 1019, 1937.

†Furnished for this study by The Lederle Laboratories, Inc.

‡Furnished by City Health Department. Made from Lot No. 491, Parke, Davis & Company.

tested gave parallel results between the patch test and the Mantoux test. All of the remaining six (6.25 per cent) showed a positive patch test and a negative Mantoux. There was only a slight difference recorded with the two types of patch tests.

TABLE II

COMPARISON BETWEEN (1) BEEF EXTRACT MEDIUM AND (2) SYNTHETIC MEDIUM MADE ACCORDING TO SIEBERT'S FORMULA

	TOTAL CASES		CASES	PERCENTAGE
(1)	48	Conformity of patch and Mantoux*	46	95.83%
		Positive patch and negative Mantoux	2	4.17%
(2)	48	Conformity of patch and Mantoux*	44	91.66%
		Positive patch and negative Mantoux	4	8.33%

*Including one case each in which recent Mantoux was positive.

Fig. 2.—Close-up of patch test.

In twenty-four cases (25 per cent of entire group) there was some reaction in the skin, due either to the control patch or to the adhesive plaster. In no instance was it marked enough to interfere with the reading and reliability of the test.

The above figures would lead one to believe that the patch test, as described by Vollmer and Goldberger, is at least as efficient as the Mantoux test when used for routine testing purposes.

In performing and recording a series like the above, several interesting and worth-while facts are noted. In the first place, many children feared the needle, but none feared the ether cleansing and adhesive tape. Secondly, numerous severe local reactions occurred following the Mantoux test. These included several cases with adenitis and occasional ones with lymphangitis. None of the patch tests produced more than transitory itching. Thirdly, the ease of application is important. The patch test can be applied rapidly, even by an inexperienced person. Contact is always obtained. There is no chance of misplacing the tuber-

culin as occurs in the Mantoux test when the needle is accidentally introduced subcutaneously because of movement on the part of the child.

A factor equally as important as the above is the availability of the patch test to the general practitioner and pediatrician. It removes the necessity of keeping O. T. in stock and also the trouble of preparing dilutions from the stock mixture. Since it comes in a dried form, it should keep indefinitely.

CONCLUSIONS

1. The tuberculin patch test of Vollmer was tried on ninety-six persons, ninety-one of whom were children in a tuberculosis sanatorium. 90 (93.75 per cent) showed conformity between the patch test and the Mantoux test in a 1:1000 dilution. The remaining 6 (6.25 per cent) showed positive patch test and negative Mantoux test.

2. The patch test was found to be as reliable as the Mantoux test.

3. Equally good results were obtained with patch tests prepared from old beef extract medium and with synthetic medium from Siebert's formula.

4. The test is painless and children do not fear it because no instruments are required.

5. Severe local and constitutional reactions do not occur, and there is no danger of infection.

6. It should prove of great service to the general practitioner and the pediatrician in the diagnosis of tuberculosis during childhood.

RELATION OF INTESTINAL BLEEDING TO HETEROTOPIC GASTRIC MUCOSA AND ULCERATION IN MECKEL'S DIVERTICULUM

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IN ORDER to elucidate the relationship of intestinal bleeding from a Meckel's diverticulum to the type of mucosa existing in the diverticulum and to the occurrence of ulceration in the mucosa, the series of surgical and autopsy cases at the Babies Hospital has been reviewed along the following lines. First, on the pathologic side, the incidence of heterotopic gastric mucosa and of mucosal ulceration, gross and microscopic, was determined in all the cases of Meckel's diverticulum in which this question had been investigated histologically or in which material was still available for suitable study. Second, on the clinical side, the occurrence of intestinal bleeding in these cases was determined from the history by checking the progress notes for hematemesis, melena, and tarry stools, from the laboratory reports by reviewing the chemical tests for blood, and from the nurses' notes by evaluating descriptions of vomitus and stools. Since this is presented as the experience of one hospital rather than as a compilation, no other reference will be made to the literature except to the work of Schullinger and Stout,[1] which carries an extensive bibliography.

Of a total of eighty-eight cases of Meckel's diverticulum in our files, nine were surgical, and seventy-nine (or an incidence of 1.3 per cent in all our autopsies) were post-mortem specimens. Clinical reports were lacking on one case in each group, leaving a total of eighty-six. Of these eighty-six cases we have complete data—clinical, gross, and microscopic pathology—in seventeen cases (nine autopsy and eight surgical). These seventeen cases form the chief basis for this report, and the findings in the remaining sixty-nine will be summarized briefly.

Of the nine autopsy cases, in all of which Meckel's diverticulum was an adventitious finding unrelated to cause of death, two contained heterotopic gastric mucosa, none exhibited mucosal ulceration, and in only one was there evidence of intestinal bleeding. In the latter case the terminal coffee ground vomitus was ascribed to uremia.

Of the eight surgical cases, five exhibited intestinal bleeding, seven contained gastric mucosa, and two were ulcerated, one grossly in the intestinal type mucosa, the other microscopically in the heterotopic gastric mucosa. There seemed a definite relationship between intestinal bleeding and heterotopic gastric mucosa, since all five bleeding cases exhibited gastric mucosa. However, two of the three nonbleeding patients also exhibited gastric mucosa. There was no definite relation of intestinal bleeding to ulceration, since of the five bleeders only one exhibited ulcera-

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tion, whereas of the three nonbleeding patients, one was also ulcerated. The one case showing ulceration of heterotopic gastric mucosa was not associated with intestinal bleeding. Thus, in the combined surgical and autopsy series of seventeen cases, ulceration was present in no case without heterotopic gastric mucosa, and of the nine cases containing heterotopic gastric mucosa, ulceration occurred in only two. In one of these latter two cases ulceration was located in the heterotopic gastric mucosa, and in the other in the intestinal type mucosa.

Thus, five of the seventeen cases exhibited intestinal bleeding attributable to no other cause than coexisting Meckel's diverticulum; nine contained heterotopic gastric mucosa; two were ulcerated. All five of the bleeders contained heterotopic gastric mucosa, but in none was it ulcerated; four of the twelve nonbleeding patients also contained gastric mucosa, which was ulcerated in one. It might be derived tentatively that if intestinal bleeding is encountered with Meckel's diverticulum, the presence of heterotopic gastric mucosa is likely.

In the sixty-nine additional autopsy cases we are justified in the main, for lack of more specific gross description and microscopic sections, only in correlating intestinal bleeding with the presence of a Meckel's diverticulum, and this only when other sources of intestinal bleeding have been ruled out. In three cases of the sixty-nine such intestinal bleeding was detected.

In summary, Table I expresses the relationship of ulceration and of heterotopic gastric mucosa to the bleeding syndrome, as shown in this series of cases.

TABLE I

HISTOLOGIC PICTURE IN MECKEL'S DIVERTICULUM, WITH RELATION TO THE BLEEDING SYNDROME

	SURGICAL CASES		AUTOPSY CASES		TOTAL
	WITH BLEEDING	WITHOUT BLEEDING	WITH BLEEDING	WITHOUT BLEEDING	
Heterotopic gastric mucosa	5	2	0	2	9
Ulceration in heterotopic gastric mucosa	0	1	0	0	1
Ulceration in intestinal type of mucosa	1	0	0	0	1
No bleeding source discovered	4	-	-	-	4
Total cases examined histologically	8		9		17

CONCLUSION

The conclusions drawn from the material available for this survey are:

1. Intestinal bleeding in the clinical syndrome Meckel's diverticulum indicated the presence of heterotopic gastric mucosa, but in our series ulceration was rarely found.

2. Heterotopic gastric mucosa was present in many cases and in a fair number occurred without intestinal bleeding.

REFERENCE

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THE NERVOUS SYSTEM IN ACRODYNIA

Review of the Literature and Report of a Case

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ALTHOUGH acrodynia has become a well-defined and fairly common clinical entity, reported examinations of the nervous system are not only somewhat meager but are conflicting. The confusion is evident not only in locating the site of the lesion, but also in the type of cellular response noted. This great variance in findings is demonstrated in the accompanying tabulation, which includes all of the available pathologic descriptions.

The original description of acrodynia was published by O. Selter[1] in 1903. In 1914 Swift[2] reported a series of cases in Australia. Since that time it has gone under a variety of names: "Selter-Swift-Feer's Disease," "pink disease," "erythroedema," "dermatopolyneuritis," "trophodermatoneurosis," and "vegetative neurosis." It appears in young children, chiefly "toddlers," and has been said to have occurred in epidemics. The onset is usually insidious. Changes in the disposition, such as apathy, may appear first. The extremities become swollen and podgy, and erythematous rashes appear on the skin. Hyperesthesias and pruritis are common. Signs of dysfunction of the autonomic nervous system include profuse sweating, digestive disorders, tachycardia and hypertension, dilatation of the pupils and photophobia, increased metabolic rate, alopecia neurotica, rhinorrhea, sialorrhea, vasomotor disturbances in the extremities, and trophic ulcers. Occasionally muscular weakness is the first symptom, and the deep reflexes often disappear. In severe cases this weakness is followed by paralysis. Pleocytosis and increase of spinal fluid protein have been noted. The prognosis is usually good, and complete recovery occurs in three to nine months. Emaciation or intercurrent infection is the cause of death in a few cases.

SUMMARY OF NEUROPATHOLOGIC CHANGES REPORTED

Spinal Cord.—Of the total of thirty-seven cases reported, nothing abnormal was noted in eighteen. Four cases showed only a slight diffuse increase of small round cells. Edema without inflammatory infiltration was observed in two cases. One case contained inflammatory nodules, consisting mostly of lymphocytes, near the entrance of the dorsal roots. Involvement of nerve cells was described in twelve cases. One of these consisted of vacuolar degeneration of posterior horn cells, one of poorly stained anterior horn cells, and one of a few swollen anterior horn cells. Distinct chromatolysis of nerve cells was cited in nine cases; in seven of these it was confined to anterior horn cells, in one to cells of the anterior horns, lateral horns, and Clarke's column, and in another to cells of the lateral horns, with lesser changes in the anterior horns.

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In eleven cases a diffuse increase of small round cells was noted, Willie and Stern reporting seven of these. Myelin sheath abnormalities were observed in only three instances, and in two of these it was mild.

No abnormalities noted		18
Slight increase of small round cells		4
Edema without inflammatory reaction		2
Inflammatory nodules		1
Nerve cell involvement		12
posterior horn cells	1	
anterior horn cells alone	9	
anterior and lateral horn cells	1	
anterior and lateral horn cells and cells of Clarke's column	1	
Total		37

Brain.—No pathologic manifestations were noted in eighteen cases. In another ten the changes were nonspecific, consisting of generalized congestion, edema, hyperemia, anemia, or slight increase of small round cells. In seven cases there was involvement of the region adjacent to the third ventricle, postulated as the site of the diencephalic sympathetic center. In two cases the lesions were widely scattered throughout various portions of the brain.

No abnormalities noted	18
Nonspecific changes, as edema and congestion	10
Involvement of sympathetic center in diencephalon	7
Scattered lesions	2
Total	37

Peripheral Nerves.—Involvement of peripheral nerves was described in twelve instances. Actual degeneration of myelin sheaths or axis cylinders was present in seven of these. Chromatolysis of cells in the gasserian ganglion was noted in two cases. In nine cases there was specific mention that no abnormalities were found in the peripheral nerves.

Sympathetic Nervous System.—The peripheral sympathetic system was involved in eight cases. In one case many nerve cells with two nuclei were found; lymphocytic infiltration was described in three cases; in two cases there was neuronophagia in addition to the lymphocytic infiltration; in another two cases there was marked neuronophagia and cellular degeneration. There is specific mention that no abnormalities were found in eight cases. There were few cases, however, in which adequate examination was made of the paravertebral chain ganglia and their peripheral connections.

Vagus Nerve.—Some degeneration was noted in one instance.

Peripheral nerve involvement	12
Sympathetic nerve involvement	8
Gasserian ganglion, chromatolysis	2
Vagus degeneration, mild	1
Dorsal root involvement	9

TABLE I

NEUROPATHOLOGIC CHANGES DESCRIBED IN ACRODYNIA

AUTHOR	SPINAL CORD AND ROOTS	BRAIN	PERIPHERAL AND SYMPATHETIC NERVES
Byfield (1920)	A few anterior horn cells stained poorly; gliosis around central canal; some variation in fiber size in lumbar posterior roots with edema and swelling of myelin sheaths.		Edema of myelin sheaths and connective tissue about nerve fibers in sciatic nerve.
Paterson and Greenfield (1923) 2 cases	Slight diffuse increase of small cells, apparently glial, in cervical and lumbosacral enlargements and in roots (especially dorsal roots).	Cortex, thalamus, and pons negative.	Vagus and cervical sympathetic nerves negative; nuclei appeared to be more numerous in brachial plexus but median nerve was negative.
	Capillary congestion and diffuse increase of small cells in cord and roots; swelling, eccentric nuclei, and chromatolysis of anterior horn cells, most marked in lumbosacral region.	Negative.	Myelin degeneration in internal and external popliteal nerves; most marked distally; some changes in lumbar nerve.
Helmholz (1925)		Negative.	Definite nerve changes.
Howland (1925)	Cord negative	Negative.	Few changes but not enough to warrant diagnosis of peripheral neuritis.
Warthin (1926) 2 cases	Cord and roots negative except for edema of meninges.	Marked congestion and edema of meninges with proliferation of reticulo - endothelial cells.	
	Perivascular edema; no degenerative or inflammatory changes.	Marked congestion and edema of brain and meninges and marked proliferation of reticulo-endothelial cells.	
Feer (Vetter) (1925)	Cord negative		Sympathetic nerves negative.
Woringer (1926)		Brain edematous; some macrophagic foci at posterior commissure of third ventricle.	Many cells in sympathetic ganglion with two nuclei, some with chromaffin granules.
Kernohan and Kennedy (1928)	Chromatolysis of anterior horn cells, especially in ventrolateral group in sacral region; lateral horn cells and cells of Clarke's column involved in thoracic region; apparent increase in glia; no one cell group completely involved; chromatolysis in posterior root ganglia, especially at lumbar level.	Advanced chromatolysis in floor of fourth ventricle, locus caeruleus, mesencephalic root of fifth nerve, lenticular nucleus, anterior nucleus of thalamus.	Myelin sheath disintegration and swollen, nodular axis cylinders, especially in sciatic and femoral nerves; marked chromatolysis in gasserian ganglia.

TABLE I—CONT'D

AUTHOR	SPINAL CORD AND ROOTS	BRAIN	PERIPHERAL AND SYMPATHETIC NERVES
Francioni and Vigi (1928) (developed after epidemic encephalitis)		Chromatolysis, eccentric nuclei, and some shadow cells in infundibulum and tuber cinereum; dissipation of lesions toward hypothalamus.	Perivascular collars of small round cells in cervical sympathetic ganglia.
Findlay and Stern (1929)	Small round cell infiltration in cord and along posterior roots; early anterior horn cell changes.	Small round cell infiltration in medulla; negative above medulla.	Cervical and abdominal sympathetic ganglia negative.
Orton and Bender (1931) (review of Byfield's case)	Chromatolysis, sclerosis, and destruction of many lateral horn cells; loss of myelin sheaths, glial increase, small hemorrhages in lateral horns; chromatolysis of anterior horn cells without glial reaction.		
Willie and Stern (1931) 7 cases	Slight anterior horn cell chromatolysis with some satellitosis in seventh cervical segment; advanced changes in anterior horn cells in fourth and fifth lumbar; slight round cell infiltration; some myelin degeneration.	Negative.	Beading and fragmentation in sciatic nerve and brachial plexus.
	Few swollen anterior horn cells; diffuse infiltration of small round cells; fat droplets in dorsal roots.	Increased vascularity of cortex; slight small cell infiltration in cortex and medulla.	Negative.
	Some anterior horn cell chromatolysis in lumbar region; small cell infiltration, especially in dorsal horns.	Small round cell infiltration in cortex and basal ganglia.	Negative.
	Slight excess of small cells.	Negative.	Negative.
	Few rounded anterior horn cells in cervical enlargement; slight chromatolysis in anteromedial group in third and fourth lumbar; small round cell infiltration.	Negative.	Fat globules along course of all peripheral nerves, especially median.
	Chromatolysis and few eccentric nuclei in anterior horn cells of lumbar enlargement; small cell infiltration.	Negative.	Early degeneration of peripheral nerves, especially near Ranvier's nodes.
	Slight increase of round cells.	Negative.	Some degeneration of vagus fibers.

TABLE I—CONT'D

AUTHOR	SPINAL CORD AND ROOTS	BRAIN	PERIPHERAL AND SYMPATHETIC NERVES
Soós (1931)		Brain substance soft, doughy, and anemic.	Marked differences in size, pyknotic and absent nuclei, poorly stained tigroid substance, and marked neuronophagia in cells of solar and paravertebral chain ganglia.
de Lange (1932)	Spinal cord negative; chromatolysis and eccentric nuclei in posterior root ganglia.	Circumscribed frontal meningitis, perivascular infiltration in pia-arachnoid; increase of glia (especially microglia) without neuronophagia in infundibulotuberous region and "gliaknötchen"; less marked glial increase in midbrain, locus caeruleus, putamen, globus pallidus, and right dentate nucleus; changes not found in controls.	Chromatolysis and eccentric nuclei in gasserian ganglion.
Bellocq and Meyer (1932)	Some degeneration and vacuolization of posterior horn cells.	Cellular lesions and neuronophagia in the infundibulotuberous region and along the walls of the third ventricle.	Numerous foci of neuronophagia and cellular degeneration in sympathetic chain ganglia; myelin degeneration in crural and intraspinal nerves.
Blackfan and McKhann (1933) 5 cases	Examination of the central nervous system, peripheral nerves, and sympathetic nervous system failed to disclose changes which could not be related to the terminal infection.		
Braithwaite (1933) 2 cases	Cord negative.	Brain injected; increase in cerebrospinal fluid; apparent increase in neuroglial cells of white matter.	
	Cord negative.	Brain congested and edematous; glia slightly edematous.	
Wolf and Davison (1934)	Chromatolysis and vacuolization in nucleus ventralis of eleventh nerve and anterior horn cells; mild disintegration of single fibers in spino-olivary, spinocerebellar, and lateral pyramidal tracts.	Slight disarrangement of all layers of cortex, especially third; some chromatolysis and falling out of cells, slight increase in glia in cortex; swelling of ganglion cells in basal ganglia; severe cell changes in locus caeruleus; absence of fibrillary processes, lack of chromatin, and swelling of Purkinje cells in cerebellum; some swelling of ganglion cells about fourth ventricle and pons.	Early disintegration and swelling of myelin, early axis cylinder changes in peripheral nerves, more advanced in lower extremities.

TABLE I—(CONT'D

AUTHOR	SPINAL CORD AND ROOTS	BRAIN	PERIPHERAL AND SYMPATHETIC NERVES
Deamer and Biskind (1934)	Spinal cord negative; chromatolysis and neuronophagia in thoracic posterior roots.	Negative.	Chromatolysis and neuronophagia in sympathetic chain ganglia with phagocytic cell infiltration resembling tubercle of rabies; sympathetic ganglia of thoracic aorta negative; slight spreading of bundles of vagus and sciatic nerves.
Fessler (1935)		Hyperemia and edema of brain; internal hydrocephalus.	
Mouriquand, Dechaume, Bernheim, and Weill (1935)	Inflammatory nodules, consisting mostly of lymphocytes, in thoracic region near entry of dorsal roots; lymphocytic infiltration and satellitosis of ganglion cells in dorsal root ganglion.	Brain congested; slight inflammation, perivascular cuffing of lymphocytes and plasma cells in meninges; nodules of lymphocytes or glia in supraoptic nuclei; vascular congestion and distention of perivascular sheaths around third ventricle.	Lymphocytic masses, perivascular cuffing, lymphocytic invasion of stroma, satellitosis and pseudoneuronophagia, and some neuronophagia in coeliac and cervical sympathetic ganglia; peripheral nerves negative.
Pehu, Dechaume, and Boucomont (1936)	Cord and roots negative.	Perivascular cuffing and lymphocytic infiltration in meninges; marked congestion, and engorgement of vessels, leucocytic thrombi in region of third ventricle; lymphoplasmocytic infiltration, as partial perivascular cuffs, near vegetative nuclei in walls of third ventricle.	Increase of lymphocytes, perivascularly and in stroma, and of satellite cells in sympathetic ganglia.
Mouriquand, Dechaume, and Sédallian (1936)	Cord negative.	Congestion of small vessels with hemorrhages in perivascular spaces in walls of third ventricle; similar changes in cerebral cortex.	Perivascular lymphocytic infiltration in coeliac ganglion.
Harris (1935)	Small round cell infiltration and well-marked chromatolysis of anterior horn cells in spinal cord.	Congestion of cortical vessels; small round cell infiltration; but no degeneration.	Patchy demyelinization in most peripheral nerves, especially in left phrenic and left sciatic nerves and in right brachial plexus; both vagi negative.

Dorsal Roots and Ganglia.—Abnormalities in the dorsal roots were present in nine cases. In four this consisted of an increase or infiltration of small round cells, in three there was chromatolysis of ganglion cells, in one fat droplets were noted, and in one there was edema.

CASE REPORT

P. R., a boy, 2 years and 10 months old, entered the hospital May 25, 1935, with bronchopneumonia. He had had a previous attack of pneumonia in December, 1934, accompanied by otorrhea and tonsillitis.

In February, 1935, he became listless, his legs became weak, and all of his extremities cold and pink, turning definitely red in a few days. His temperature was slightly elevated. There was profuse sweating. When he was placed on his feet, he showed evidence of discomfort. Later in the month his feet scaled, and the distal phalanges of the fingers became swollen and puffy. He slept in grotesque positions and was very irritable. His appetite was poor, and he lost a slight amount of weight. During March he became somewhat worse. In April an abscess developed in the right ear and was drained. Swelling of the hands increased and also appeared in the feet. The child was unable to walk. During the next month the paralysis increased and involved both arms and legs. The pink color disappeared. On May 23 a cough developed, he became prostrated, breathing became difficult, and the temperature rose to 102.2° F., dropping to 101.6° F. the next day when he entered the hospital.

Physical Examination.—He was a well-developed but malnourished boy, breathing rapidly and coughing frequently. There was marked scaling and thickening of the epidermis of the extremities. The tonsils were reddened but not enlarged. The percussion note was dull over the entire right side of the chest; the breath sounds were diminished and were bronchial in character posteriorly. X-ray films revealed collapse of the right middle and upper lobes.

The neurological examination showed a flaccid paralysis of both legs with absent knee and ankle jerks. No pathologic reflexes were elicited. Both biceps and triceps reflexes on the right were not obtained. There was marked weakness of both upper extremities. The electrical reactions of the muscles were not impaired. The abdominal and cremasteric reflexes were absent. There was marked hyperalgesia.

Blood Count.—5,300,000 red cells; 95 per cent hemoglobin; 47,800 white cells, with 85 per cent polymorphonuclears, of which 29 per cent were banded.

Course.—During the next few days he improved; the right lung expanded, and the white count decreased to 26,000 on May 29. But on June 1 the respiratory rate increased, the right lower lobe collapsed, and a mucous rattle was audible. Carbogen was given, but on the morning of June 2 the patient suddenly died. No cyanosis was present.

Autopsy.—Sections of skeletal muscle from the back, pectoral muscles, and diaphragm were normal. There was a slight fatty infiltration of the heart, but the muscle fibers were normal. Sections through the aorta were negative. Hassall corpuscles were quite numerous in the thymus; the cellular elements were normal. The lungs were moderately congested, and there were a few areas of collapse. In places the alveoli were filled with fluid and contained large mononuclears, lymphocytes, and polymorphonuclear leucocytes. The bronchi contained desquamated epithelial cells, a few lymphocytes and polymorphonuclears, and red cells; the mucosa was moderately infiltrated. Smears from the right middle lobe contained gram-positive cocci in pairs and short chains; no acid-fast bacilli were seen. A peribronchial lymph node was moderately congested and contained many leucocytes; the germinal centers were large and several mitotic figures were present.

Nothing abnormal was present in the gastrointestinal tract. The capsule and trabeculae of the spleen were normal; some large phagocytic cells in the pulp contained a small amount of brown pigment. Adrenal cortical cells contained moderate amounts of lipoid material.

Examination of the Nervous System.—Examination of the coeliac ganglion revealed nothing abnormal. Unfortunately no other part of the sympathetic nervous system and none of the peripheral nerves were available for examination.

Macroscopically there were no abnormalities in either the brain or spinal cord.

Celloidin sections were made from various portions of the brain and spinal cord. Nothing abnormal was found in the cortex, mesencephalon, pons, cerebellum, or medulla. Serial sections of the diencephalon from the level of the subthalamic nucleus through the tuber cinereum were studied. Careful examination was made of the paraventricular nucleus, the supraoptic nucleus, the nucleus of the tuber cinereum, the mammillary body, and the subthalamic nucleus (corpus luysi). There was no perivascular infiltration or increase of glia. Many of the cells contained eccentric nuclei and only small amounts of Nissl substance; pseudoneuronophagia was present in places. Such findings, however, were interpreted as normal in this portion of the brain. There was no true neuronophagia. The nuclei were of regular contour, the nuclear membranes were intact, and the nucleoli were not pyknotic. The cells were neither swollen nor shrunken, and no shadow forms were present.

In the spinal cord, sections through the cervical region were normal. The intermediolateral cell column in the thoracic region contained many degenerating cells. Extrusion of the nucleus, folding of the nuclear membrane, absence of Nissl bodies, vacuole formation, and occasional shadow forms were observed (Fig. 1). The cells of Clarke's column were larger than the anterior horn cells at the same level, and degenerative changes were seen in a few of them. Anterior horn cells in the cervical, thoracic, and upper lumbar segments were normal. The most striking changes were present in the lower lumbar and upper sacral regions, involving the anterior horn cells of the posterolateral cell column (Fig. 2). There were many round and swollen cells, marked central chromatolysis, eccentric nuclei, and vacuole formation. The nuclear membranes were often hyperchromatic and folded and the nucleoli pyknotic. In some cells the nuclei were missing or protruding. Shadow forms indicated advanced degeneration. Compared with the amount of cellular involvement, there was but little glial response. Satellitosis and neuronophagia were seen only in a few places. Frozen sections stained with the Cajal gold-sublimate method revealed no increase in neuroglia. No myelin sheath abnormalities were present with the Weigert stain.

DISCUSSION

The clinical picture of acrodynia clearly points in all cases to an involvement of the sympathetic nervous system. The symptomatology is so widespread that this involvement must necessarily be either localized in a center of sympathetic activity, as in the diencephalon, or diffuse throughout more peripheral portions of the sympathetic system. Pathologic changes have been located by various authors in the following places: (1) the diencephalic sympathetic centers, (2) the intermediolateral cell column in the spinal cord, (3) the paravertebral chain ganglia and the other peripheral sympathetic nervous pathways, and (4) the peripheral nerve trunks and posterior roots.

Francioni and Vigi,[10] de Lange,[15] and Bellocq and Meyer[16] described lesions in the region of the tuber cinereum and infundibulum; Mouriquand, et al,[22] noted inflammatory lesions in the region adjacent to the

third ventricle. Orton and Bender[12] found the most marked changes in the intermediolateral cell column, in which sympathetic motor cells

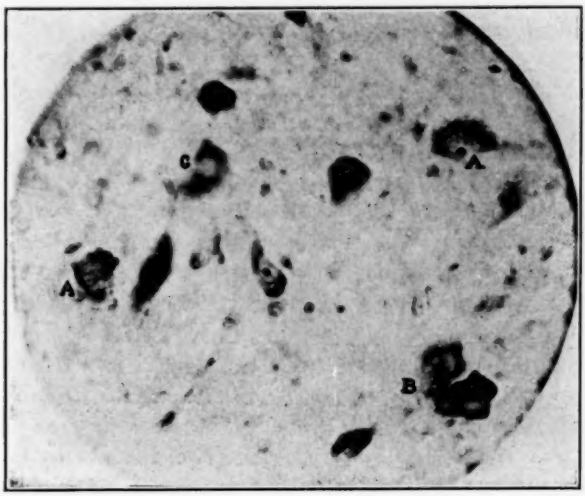

Fig. 1.—Extruding nuclei (A) and degenerated cells with absent nuclei (B) in intermediolateral cell column. A cell which is not in focus (C) contains a large vacuole. Cresyl violet stain.

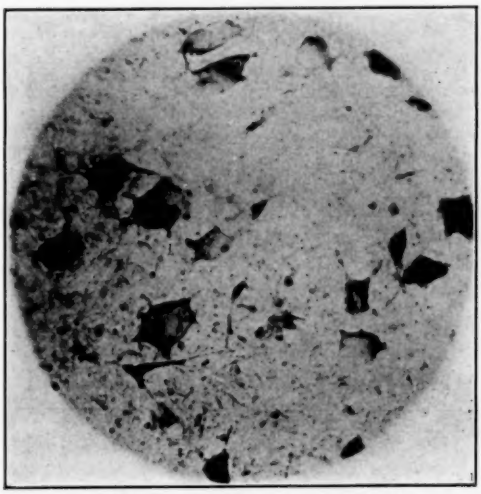

Fig. 2.—Anterior horn cells of the posterolateral cell column in the upper sacral region, showing marked swelling, chromatolysis, eccentric nuclei, and shadow forms. Cresyl violet stain.

form synapses with descending sympathetic pathways in the spinal cord and give off sympathetic neurones to the peripheral sympathetic ganglia. Kernohan and Kennedy[9] also noted involvement of this re-

gion, although merely as part of widespread damage. Soós[14] and others described neuronophagia in paravertebral and other sympathetic ganglia. Paterson and Greenfield[4] believed that the disease was a polyneuritis. Varying degrees of posterior root involvement were mentioned in nine cases.

Those findings in the diencephalon particularly warrant skepticism. Schwarz, Goolker, and Globus[24] have pointed out normal findings in infants' brains that are frequently misinterpreted as pathologic. This was in an attempt to disprove Goldzieher's theory that intestinal intoxication of infants (Goldzieher's "diencephalitis dehydrans") was due to cellular infiltration of the region adjacent to the walls of the third ventricle. They observed that discrete cellular aggregations, often perivascular, in this region were but normal manifestations of a ripening brain.

In the case described here interest was particularly focused on the diencephalic sympathetic nuclei. Serial sections through this region, including the subthalamic nucleus, the periventricular nuclei, and the tuber cinereum, failed to reveal anything which could be interpreted as pathologic. Eccentricity of nuclei and lack of centrally placed Nissl bodies were considered as normal in this area. Pathologic findings were all confined to the spinal cord. Involvement of anterior horn cells in the lumbosacral region and of cells of the intermediolateral cell column in the thoracic region were noted, the changes being especially striking in the anterior horn cells. These changes consisted of swelling and central chromatolysis, folding of the nuclear membrane, nuclear displacement, and shadow forms, but there was no marked glial reaction. Changes in the anterior horn cells explain the flaccid paralysis found in this case. The changes in the intermediolateral cell column, in which are located sympathetic motor cells, seem significant. In only two other cases (Kernohan and Kennedy[9] and Orton and Bender[12]), however, have similar changes been noted, so that it is difficult to evaluate whether they are of fundamental importance.

A review of the literature shows that reported changes in the nervous system are inconstant. Degenerative changes in anterior horn cells, as noted in this case, were lacking in many reports. For example, in Willie and Stern's series[13] of seven cases chromatolysis was not noted in two, was mild in four, and was advanced in only one case. In the same series varying degrees of peripheral nerve involvement were found in four cases, and there were no changes in three; in two of the cases small cell infiltration in the cerebrum was mentioned and was not found in five.

Failure in finding constant and fundamental pathologic changes, however, is not without precedent in diseases of the nervous system. Honeyman[25] has reported four fatal cases of acute febrile polyneuritis

(or neuronitis) in which a detailed and systematic histopathologic examination failed to reveal any significant changes. The etiology of this condition, as is the case with acrodynia, is not known. There is evidence indicating that infections or toxins may ascend in the perineural lymph spaces and pass through large areas of the nervous system without leaving behind evidence that is demonstrable by modern methods.

A glance at the summary of the pathologic studies will make it clear that many of them have not been systematic or thorough. The vascular changes, forming so constant and characteristic a feature of the clinical picture, suggest that alterations in the sympathetic fibers of the peripheral blood vessels might be found, but they apparently have not been sought. Detailed studies of all of the sympathetic ganglia have rarely been made. This is, of course, the more surprising since the constant and characteristic features of the disease are those of disturbed sympathetic function. The present study will best serve its purpose if it encourages more detailed examinations of the entire nervous system, with special emphasis on its autonomic components. While previous studies and the present one have failed to show any constant lesions, either in occurrence, character, or distribution, nevertheless nervous lesions have been noted frequently enough to indicate quite strongly that a specific etiologic agent with special effects on the nervous tissues actually exists. Since clinically the disease appears to be of an infectious nature, further search is certainly desirable for a specific virus or perhaps a bacterial agent with toxic properties.

SUMMARY

1. The findings in the nervous system in a case of acrodynia are reported.

2. No pathologic changes were found in serial sections through the diencephalic sympathetic nuclei. This fails to support the belief that this region is the primary focus of involvement.

3. Degenerative changes were present in the anterior horn cells of the lumbosacral region and in the intermediolateral cell column of the spinal cord.

4. A review of the literature and the data supplied by the present case show that while alterations in the nervous system are not infrequently observed, they are not constant in occurrence, kind, or localization and hence do not offer a satisfactory explanation of the clinical picture.

5. Since the latter, nevertheless, quite consistently points to a disturbance in the sympathetic nervous system, it is desirable that further and more systematic search for lesions in this system be made.

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SULFANILAMIDE IN THE TREATMENT OF GONORRHEAL OPHTHALMIA IN CHILDREN

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SINCE the introduction of the Credé method of prophylaxis, the incidence of ophthalmia neonatorum has not diminished to the extent that many anticipated. Ernst Fuchs, in 1884,[1] reported the statistics of Credé to the effect that the incidence of this disease had diminished from 10.8 per cent to 0.1 to 0.2 per cent following the introduction of the use of silver nitrate. More recent information has shown that ophthalmia neonatorum is responsible for more cases of blindness today than from any other affection. McKee[2] states that 10 per cent of the 300,000 blind persons in Europe and 30 to 60 per cent of all those in asylums were rendered so by this disease. Surveys by Mayou[3] in London have shown that the number of cases has not materially decreased in a fifteen-year period. Lehrfeld[1] found a similar situation in Philadelphia; the Department of Public Health records investigated showed no diminution despite the generalized application of the Credé method of antisepsis. In those hospitals in which ante-partum antisepsis of the expectant mother known to have gonorrhea was carried out, there was not a single case of ophthalmia. Hospitals using no prenatal antisepsis showed 43.7 failures per 1,000 births, with a total of 535 cases. The inference is that the Credé method of prophylaxis is not being carried out as originally described and is in need of revision to include antisepsis of the Neisserian-infected mother.

Ophthalmia occurs more frequently in infants than in adults, probably on the basis of the less effective mechanical barrier that is present. The cornea of the infant is only three cells in thickness, the ocular conjunctiva is much thinner than in adults, and with the mucoid changes occurring as a result of infection, the basement membrane is bared, allowing a ready entrance of organisms to the subconjunctival tissues. At birth there is little or no lymphoid tissue in the conjunctiva. There is a gradual increase in this type of tissue, but the rapidity with which it forms is dependent upon the amount of irritation present. This explains the thickened conjunctiva which occurs in the chronic state of ophthalmia.

Stephenson[4] reviewed the subject of ophthalmia thirty years ago and concluded after a thorough study of the literature that two-thirds

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I wish to acknowledge the suggestions of Dr. H. L. Begle.

of all cases in the newborn infant were due to the gonococcus. May[5] agrees with these figures. In Bellows' series[6] of 188 cases, 45 per cent were due to the gonococcus. Thygeson,[7] however, found an incidence of less than 0.03 per cent in a series of 261 cases of ophthalmia neonatorum. He points out the common diagnostic error of confusing staphylococcus conjunctivitis and inclusion blenorrhea with gonorrheal ophthalmia. *Staphylococcus aureus* is the most frequent cause of abundant purulent secretion and mild conjunctival infiltration. This condition responds rapidly to treatment, in contradistinction to inclusion blenorrhea and gonorrheal ophthalmia. Thomas[8] reports 100 consecutive cases of purulent conjunctivitis in the newborn infant caused by a single strain of *Staphylococcus aureus,* probably transmitted by contamination.

During the last few years there has been nothing significant reported in the treatment of gonorrheal ophthalmia. Many of the commonly employed antiseptics are of little or no value in shortening the duration of the disease. Bellows has shown that argyrol, mercuric oxycyanide, and metaphen are without great beneficial effect in shortening the course of the disease. He found acriflavine 1:1,500 the most efficacious of the antiseptics tried.

Opinion varies concerning the value of gonococcal vaccines. Many writers, as McKee, state that vaccines are equal but in no way superior to whole milk. Mayou concludes that such vaccines are without any influence in shortening the duration of the disease.

There is also a divergent view concerning the value of foreign protein in the treatment of the ophthalmias. Brewster[9] has found them efficacious in the treatment of corneal ulcers. Hektoen[10] objects to the widespread and indiscriminate use of nonspecific foreign protein therapy as whole milk on the grounds that it may give rise to more or less permanent sensitizations. Bernstein[11] reports specific sensitization following the use of milk and advocates instead the use of a protein not closely related to the dietary or environmental proteins. It would seem wise to reduce all foreign protein administrations to a practical minimum.

In view of the numerous inadequacies of our present forms of therapy, any treatment which will reduce the length of hospitalization and decrease complications is acceptable. Following the accounts of Domagk[12] and later of Long,[13] Dees and Colston[14] were the first in this country to report on the use of sulfanilamide in the treatment of gonococcic infections. Marshall[15] showed that sulfanilamide is rapidly absorbed from the gastrointestinal tract, entering practically all the body fluids, and is excreted almost entirely in the urinary tract. Concerning its mode of action, Long[16] concluded that bacteriostasis occurs with sulfanilamide. Mellon[17] found no indication that phagocytosis is a factor in the mechanism of the drug.

Following favorable isolated reports and realizing the close relationship of the gonococcus to the meningococcus, we started the use of sulfanilamide in cases of gonorrheal ophthalmia. We have included in this series only cases of proved gonorrheal origin, determined by direct smear of the conjunctival scrapings or by culture on chocolate agar medium.

We have taken cases treated in the two-year period prior to the use of sulfanilamide as a control. These cases had repeated positive smears and were treated as follows:

1. Warm boric irrigations sufficient to keep the eyes free of discharge; irrigations were carried out every thirty minutes or more often as needed and decreased as the discharge diminished.

2. Instillation of antiseptics: argyrol, 20 to 25 per cent, was used every three to four hours after the irrigation.

3. Ice compresses were used only in cases with marked swelling and tumefaction of the lids. Care was used to avoid corneal maceration that accompanies the prolonged use of cold. Premature infants did not receive such treatment.

4. Silver nitrate, 1 per cent, was used in the more chronic cases with papillary thickening of the palpebral conjunctiva. Applications were made to the everted lids once daily.

5. Atropine sulfate, ½ to 1 per cent, was used in patients with marked spasm or corneal involvement.

6. Special measures, as external canthotomy and conjunctival flaps, were carried out as the case demanded. One group of four patients received foreign protein therapy in the form of sterile milk.

7. Daily eye smears were taken, and when three consecutive negative smears were obtained, the clinical examination giving support, the patient was removed from the isolation of the ophthalmia ward.

The control group consisted of thirty-two patients with an average hospital duration of 28.5 days. Four patients had corneal involvement, two going on to perforation. Eighteen patients had involvement of both eyes. There were twenty white patients and twelve negroes. Of the entire group, there were seven illegitimate children. There were no positive serologic findings in the entire group (many of the Kahn tests, however, were taken in children prior to the third month of life). Of eighteen females, six had positive vaginal smears. The ages of the patients varied from 1 day to 10 years.

Four additional patients were treated by sterile milk with an average hospital duration of 16.5 days; of these, none showed corneal involvement.

The children treated with sulfanilamide had an identical local care as outlined above, except that silver nitrate was not used. Sulfanilamide was given on the approximate dosage basis of one grain per

TABLE I

CONTROLS

Average Hospitalization: 28.5 Days

CASE NO.	AGE	RACE, SEX	HISTORY	ADMITTED	DISCHARGED	DURATION	OD	OS	CORNEA	NOTES
1. 120873	2 D.	W-F	1 day	12/ 4/34	1/10/35	8 days	+	–		Premat-Credé
2. 120915	2 D.	W-M	1 day	12/12/34	2/ 2/35	33 days	–	+		
3. 121384	7 D.	C-F	5 days	12/21/34	2/ 7/35	32 days	+	+		Credé Proph.
4. A-776	6 D.	W-M	?	2/ 1/35	3/21/35	31 days	+	+	+ O.U.	Illegitimate
5. A-1485	5 D.	W-F	2 days	3/ 3/35	4/ 5/35	29 days	+	+		Credé Proph.
6. A-1699	9 Yr.	W-F	8 days	3/13/35	4/ 2/35	18 days	–	+		Vaginitis
7. A-2191	14 D.	W-M	14 days	3/21/35	4/24/35	29 days	+	+		Mother's smear positive for gonococcus
8. A-3397	2 Yr.	W-F	14 days	5/ 4/35	6/17/35	39 days	+	+		
9. A-3407	6 D.	C-F	?	5/ 6/35	5/29/35	20 days	–	+		Canthotomy vaginitis
10. A-4973	16 D.	W-F	10 days	6/24/35	7/ 2/35	7 days	+	–		Illegitimate
11. A-6593	2 Yr.	W-M	3 days	8/16/35	9/ 6/35	21 days	+	+		Vaginitis
12. 88882	10 Yr.	W-F	2 days	8/16/35	9/19/35	34 days	+	+		Vaginitis
13. A-7194	9 D.	W-M	7 days	9/14/35	10/11/35	27 days	+	+		
14. B-6527	3 W.	C-M	?	9/21/35	10/ 9/35	11 days	+	–		Illegitimate
15. A-7262	3 D.	W-F	?	9/26/35	10/16/35	21 days	+	+		Illegitimate
16. A-7842	4 D.	W-M	2 days	10/16/35	12/ 1/35	30 days	+	+	+	
17. 109028	2 Yr.	C-F	21 days	10/24/35	11/28/35	15 days	–	+		Vaginitis
18. A-8296	4 D.	W-M	3 days	10/26/35	12/13/35	47 days	+	–		
19. A-8307	17 Mo.	C-M	2 days	10/28/35	11/21/35	25 days	+	–		
20. A-8856	7 D.	W-M	7 days	11/12/35	1/ 5/36	32 days	–	+		Strep. otitis media
21. B-17	8 D.	W-F	3 days	1/ 4/36	3/11/36	65 days	+	+		
22. B-308	5 D.	C-M	2 days	1/23/36	2/ 2/36	10 days	+	+		Illegitimate
23. B-400	4 D.	W-M	1 day	1/31/36	4/ 8/36	64 days	+	+	+ perf.	
24. 115608	2 Yr.	C-F	5 days	3/25/36	4/ 9/36	15 days	+	+		Vaginitis
25. B-2698	1 D.	C-F	1 day	4/ 3/36	6/18/36	61 days	–	+		Premature
26. B-3435	8 Mo.	C-F	2 days	5/11/36	6/11/36	16 days	+	+		
27. B-3162	4 Mo.	W-F	1 day	7/ 9/36	8/20/36	41 days	+	+		
28. B-5130	1 D.	W-F	1 day	7/17/36	10/15/36	34 days	+	+		Premature
29. C-6836	1 Mo.	C-M	?	10/22/37	11/ 3/37	13 days	+	–	+ perf.	
30. C-986	4 D.	W-F	?	2/ 7/37	4/ 6/37	26 days	+	+		
31. C-2101	1 Mo.	C-M	14 days	3/16/37	4/22/37	37 days	+	+		Illegitimate
32. C-3007	1 D.	C-F	1 day	4/28/37	6/ 3/37	23 days	+	–		Illegitimate

D: days Yr: year OS: left eye W: white M: male
Mo: months OD: right eye Perf: perforation C: colored F: female

TABLE II

SULFANILAMIDE

Average Hospitalization After Sulfanilamide Started: 5.8 Days

CASE NO.	AGE	RACE, SEX	HISTORY	ADMITTED	DISCHARGED	DURATION	OD	OS	CORNEA	NOTES
1. C-3583	23 Mo.	C-F	1 day	5/28/37	6/10/37	11 days	+	-		Rickets
2. C-4292	1 Mo.	W-M	1 mo.	6/28/37	7/10/37	6 days	+	+		
3. C-4445	21 D.	C-F	10 days	7/ 6/37	7/10/37	4 days	+	+		
4. C-4799	6 D.	C-M	3 days	7/20/37	7/25/37	5 days	+	-		
5. C-5258	9 D.	W-F	5 days	8/ 9/37	9/ 9/37	7 days	-	+		Premature
6. C-5265	3 Yr.	W-F	9 days	8/10/37	8/22/37	11 days	-	+	+	Vaginitis
7. C-6368	1 Mo.	W-M	1 mo.	9/25/37	10/19/37	5 days	+	-	+	
8. C-7450	11 Mo.	C-M	3 days	11/ 8/37	11/16/37	5 days	+	+		
9. C-7465	3 Yr.	C-M	1 day	11/11/37	11/19/37	7 days	-	+		
10. C-7548	10 D.	W-M	6 days	11/14/37	11/19/37	4 days	-	+		
11. C-7817	7 D.	C-M	1 day	11/18/37	12/ 8/37	4 days	+	+		Premature
12. C-7972	5 D.	W-M	3 days	11/30/37	12/ 7/37	5 days	-	+		
13. C-8385	12 D.	C-F	3 days	12/15/37	1/10/38	5 days	+	+		Premature
14. C-8425	12 D.	W-F	4 days	12/21/37	12/25/37	4 days	-	+		
15. A-3537	21 D.	C-F	10 days	1/ 1/38	1/ 5/38	4 days	+	+		

See footnote at bottom of Table I.

pound body weight daily, combining it with equal amounts of sodium bicarbonate. The drug was incorporated in karo water feedings with smaller infants, with no difficulty encountered by this mode of administration. Older children were given oral administration; one resistant child was gavaged. In no instance was parenteral administration found necessary. Sulfanilamide blood level determinations were made according to the method described by Marshall.[18] The levels found were much lower as a group than with older children on a similar dosage basis. Blood levels taken in the morning after a nocturnal period with no drug administration were uniformly low. Levels taken during or within a few hours after a day's administration were higher.

Fifteen patients were treated with sulfanilamide with an average hospital duration of 5.8 days. The ages of the patients varied from 5 days to 3 years. Of these, two showed corneal involvement; perforation did not result after sulfanilamide was started. Six of the group showed bilateral involvement. There were seven white and eight negro patients, seven females and eight males. One had vaginal involvement.

None of the complications attributed to sulfanilamide were observed in this group; no appreciable acidosis or cyanosis was observed. No cases showed a morbilliform rash; no nausea or vomiting was encountered.

TABLE III

SUMMARY OF TREATMENT

NO. OF CASES	TREATMENT	AVERAGE DURATION
32	Routine	28.5 days
4	Routine + milk	16.5 days
15	Routine + sulfanilamide	5.8 days*

*After sulfanilamide was started.

PRESENTATION OF CASES

CASE 1.—P. F., C-3853, colored female, aged 23 months, weight, 16½ pounds, was admitted May 28, 1937, and discharged June 10, 1937. Pain, swelling, and discharge developed in the right eye two weeks prior to admission. No home treatment was given. There was no definite history of contact.

On admission examination showed that there was massive chemosis of the right eye, with a thick, yellow, purulent discharge. The palpebral conjunctiva was edematous and injected; the cornea was clear. The left eye was apparently uninvolved. Examination revealed a malnourished, colored female child, not acutely ill. Clinical signs of active rickets were present. Direct smears of both eyes showed gram-negative intracellular and extracellular diplococci. The patient was isolated and the usual treatment instigated. In addition sulfanilamide and sodium bicarbonate were given in equal amounts. There was a rapid subsidence of symptoms, and three consecutive negative smears were obtained by the eleventh day (Table IV). On June 15, 1937, the patient had a recurrence of symptoms in the right eye, but three smears were negative. She was seen one week later with no involvement or discharge. Tuberculin test (1:5000) was negative, as well as Kahn test and vaginal smears.

TABLE IV

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
5/28	+	+	++++	–	0	
5/29	+	+	+++	–	15 gr.	
5/30	–	–	++	–	15 gr.	
5/31	–	–	+	–	15 gr.	
6/1	–	–	–	–	15 gr.	4.5 mg.
6/2	–	–	–	–	15 gr.	
6/3*	–	–	–	–	15 gr.	
6/4	+	+	–	–	15 gr.	
6/5	–	–	–	–	10 gr.	
6/6	–	–	–	–	10 gr.	
6/7	–	–	–	–	0	
6/8	–	–	–	–	0	

*Blood count: Hb. 12 gm.; R.B.C. 4,000,000; W.B.C. 9,400; polymorphonuclears, 62 per cent; small lymphocytes, 23 per cent; large lymphocytes, 15 per cent.

CASE 2.—S. W., C-4292, white male, aged 4 weeks, weight 5½ pounds, was admitted June 28, 1937 and discharged July 10, 1937 (Table V).

This child was born at the Armour Hospital, Ferndale, premature seven months. Discharge was noted in both eyes on the third day. On admission to the hospital, the patient showed swollen lids; palpebral conjunctivae, thickened and beefy with a copious, thick, yellow purulent discharge present in both eyes. The mother had a vaginal discharge during the last four months of pregnancy. Sulfanilamide was started on the sixth day after repeated positive smears. Discharge rapidly ceased, and smears were negative on the third day. A checkup two weeks after discharge from the hospital showed no recurrence, and the palpebral conjunctivae had lost all thickening. Kahn test was negative.

TABLE V

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
6/28	–	+	++	++		
6/29	+	–	++	++		
6/30	+	+	+	+		
7/1	+	+	+	+		
7/2	+	+	+	+		
7/3	+	+	+	+	5 gr.	
7/4	–	–	–	–	5 gr.	
7/5	+	+	–	–	5 gr.	
7/6	–	–	–	–	5 gr.	
7/7	–	–	–	–	5 gr.	
7/8	–	–	–	–	5 gr.	Trace*
7/9	–	–	–	–	5 gr.	
7/10	–	–	–	–	0	

*Blood level taken in the morning after a night with no administration.

CASE 3.—C. J., C-4445, colored female, aged 3 weeks, weight 7½ pounds, was admitted July 6, 1937 and discharged July 12, 1937 (Table VI).

The child was born at home; no prophylaxis was used. At 1 week of age, the right eye began to discharge; three days later the left eye became involved. On admission both lids were swollen. The conjunctivae were reddened and the corneas were clear. Marked photophobia and lacrimation was present. Smears taken were positive. Sulfanilamide was started on the second day following admission. Dis-

charge ceased, and smears promptly became negative. Patient was discharged on the seventh day with complete subsidence of involvement. Kahn test was negative.

TABLE VI

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	LEFT EYE	RIGHT EYE	RIGHT EYE	LEFT EYE		
7/6	+	+	++	++		
7/7	+	+	+	–	5 gr.	
7/8*	–	–	–	–	5 gr.	
7/9	–	–	–	–	5 gr.	1.5 mg.†
7/10	–	–	–	–	5 gr.	
7/11	–	–	–	–		
7/12	–	–	–	–		

*Blood count: Hb. 13 gm.; R.B.C. 3,930,000; W.B.C. 5,500; polymorphonuclears, 60 per cent; small lymphocytes 36 per cent; large lymphocytes, 4 per cent.
†Blood level taken in the morning.

CASE 4.—C. D., C-4799, colored male, aged 6 days, weight 5 pounds, was admitted July 20, 1937 and discharged July 25, 1937 (Table VII).

The child was born at home, attended by a midwife, and was referred by the Board of Health with a history of purulent discharge from one eye for three days. Patient showed an edematous right eye, swollen lids, and purulent discharge. Palpebral conjunctiva was injected; cornea was clear. Left eye was apparently not involved. Smears were positive, and sulfanilamide was started on the second day with rapid clearing of the discharge and subsidence of all conjunctival involvement. The child was seen on July 27, 1937, and on Aug. 2, 1937, at which times there was no involvement. Kahn test was negative.

TABLE VII

DAYS	SMEARS		DISCHARGED		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
7/20	+	–	+++	–	5 gr.	
7/21	+	–	++	–	5 gr.	5.3 mg.
7/22	–	–	+	–	5 gr.	2.5 mg.
7/23*	–	–	–	–	5 gr.	
7/24	–	–	–	–	0	
7/25	–	–	–	–	0	trace

*Blood count: Hb. 14 gm.; R.B.C. 4,800,000; W.B.C. 12,000; polymorphonuclear, 70 per cent; small lymphocytes, 28 per cent; large lymphocytes, 2 per cent.

CASE 5.—G. G., C-5258, white female, aged 9 days, weight 4½ pounds, was admitted Aug. 9, 1937 and discharged Sept. 9, 1937 (Table VIII).

The patient was born in a Dearborn hospital, seven months premature. Credé prophylaxis was used. On the fourth day discharge started in the left eye and continued to discharge in increasing amounts since then. The patient was admitted with a copious, yellow discharge, with moderate edema and papillary swelling. The child, otherwise, was a normal, well-developed, premature baby with no significant physical findings. Smears were positive for gram-negative diplococci. On the third day after admission sulfanilamide was started. Negative smears were obtained five days later and remained negative. The child was transferred to the Medical Service and remained in the hospital until it reached the weight of 5 pounds. On final discharge the eyes showed no recurrence of symptoms. Vaginal smears and Kahn tests were negative.

TABLE VIII

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
8/9	–	+	–	++		
8/10	–	+	–	++		
8/11*	–	+	–	++	5 gr.	0
8/12	–	+	–	++	7½ gr.	
8/13	–	+	–	+	7½ gr.	4.3 mg.
8/14	–	+	–	+	7½ gr.	
8/15	–	–	–	–	7½ gr.	
8/16	–	–	–	–	7½ gr.	
8/17	–	–	–	–	7½ gr.	

*Blood count: Hb. 14.6 gm.; R.B.C. 4,300,000; W.B.C. 9,400; polymorphonuclears, 65 per cent; lymphocytes, 34 per cent; basophiles, 1 per cent.

CASE 6.—R. M. W., C-5265, white female, aged 3 years, weight 22 pounds, was admitted Aug. 10, 1937 and discharged Aug. 22, 1937 (Table IX). This patient was the daughter of circus performers. The mother, an acromegalic dwarf of 41 inches, was delivered by cesarean section. Three weeks prior to admission the patient developed a profuse vaginal discharge and was treated at St. Luke's Hospital, Milwaukee, Wis. When the parents changed location the patient was seen in the out-patient department. At this time there had been a discharge from the left eye for at least twelve days. Both eyes had swelling of the lids with a purulent discharge present. The corneas were uninvolved. Physical examination showed nothing remarkable save the eye involvement and a vaginal discharge. The patient was started on sulfanilamide. On the fourth day, despite the clearance of much of the injection and edema, the left cornea showed ulcerative changes. Atropine, 1 per cent, was started, and sterile milk was also given in doses of 2 and 3 c.c. on Aug. 14, 1937, and Aug. 16, 1937. Sulfanilamide was continued at the initial dosage of 30 grains daily. Owing to the lack of cooperation, gavage feedings became necessary. She had an excellent febrile reaction to the foreign protein and a rapid clearing of the corneal ulcer by the seventh day. Daily vaginal smears throughout her entire course failed to show gram-negative cocci. Kahn test was negative.

TABLE IX

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
8/10*	–	+	–	++++	30 gr.	
8/11	–	+	–	+++	15 gr.	
8/12	–	+	–	ulcer	30 gr.	
8/13	–	+	–	++	30 gr.	11.2 mg.
8/14	–	+	–	+	30 gr.	
8/15	–	–	–	+	30 gr.	
8/16	–	–	–	+	30 gr.	7.2 mg.
8/17	–	+	–	–	30 gr.	
8/18	–	–	–	–		
8/19	–	–	–	–		
8/20†	–	–	–	–		
8/21	–	–	–	–		
8/22	–	–	–	–		

*Blood count: Hb. 11 gm.; R.B.C. 4,240,000; W.B.C. 9,600; polymorphonuclears, 74 per cent; lymphocytes, 24 per cent; eosinophiles, 2 per cent.

†Blood count: Hb. 11.5 gm.; R.B.C. 4,000,000; W.B.C. 12,400; polymorphonuclears, 66 per cent; lymphocytes, 30 per cent; monocytes, 4 per cent.

CASE 7.—R. B., C-6368, white male, aged 4 weeks, weight 5¾ pounds, was admitted Sept. 25, 1937 and discharged Oct. 19, 1937 (Table X). The child was born at the Florence Crittenden Hospital, seven months premature, and received Credé prophylaxis. Shortly after birth the eyes began to discharge, and despite routine treatment discharge continued with no abatement. Smears taken prior to admission were positive on several occasions. On the fifth day after admission corneal ulceration was noted and 1 c.c. of sterile milk was given, with no subsequent improvement. On the fifteenth day sulfanilamide was started, with a rapid cessation of discharge and a healing of the ulcer. Patient was seen one week and three weeks after discharge, with normal conjunctiva and a leucomatous patch at the site of the ulcer. Kahn test was negative.

TABLE X

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
9/26	+	–	+	–		
9/27	+	–	+	–		
9/28	+	–	+	–		
9/29*	+	–	+	–		
9/30	+	–	ulcer	–		
10/1	+	–	+	–		
10/2	+	–	+	–		
10/3	+	–	+	–		
10/4	+	–	+	–		
10/5	+	–	–	–		
10/6	+	–	–	–		
10/7	+	–	–	–		
10/8	+	–	–	–		
10/9	+	–	–	–		
10/10	+	+	–	+		
10/11	+	+	–	+	5 gr.	
10/12	+	–	–	–	5 gr.	
10/13	–	–	–	–	5 gr.	
10/14	–	–	–	–	5 gr.	4.6 mg.
10/15	–	–	–	–	5 gr.	
10/16	–	–	–	–		

*Blood count: Hb. 12.5 gm.; R.B.C. 5,200,000; W.B.C. 11,300; polymorphonuclears, 72 per cent; lymphocytes, 28 per cent.

TABLE XI

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
11/8	+	+	++	++++	20 gr.	
11/9*	+	+	+	++	30 gr.	
11/10	–	–	+	+	30 gr.	
11/11	–	–	–	–	30 gr.	5.0 mg.
11/12	–	–	–	–	30 gr.	
11/13	–	–	–	–	30 gr.	
11/14	–	–	–	–	10 gr.	
11/15	–	–	–	–		
11/16†	–	–	–	–		

*Blood count: Hb. 12 gm.; R.B.C. 3,900,000; W.B.C. 11,600; polymorphonuclears, 63 per cent; small lymphocytes, 20 per cent; large lymphocytes, 14 per cent; monocytes, 3 per cent.

†Blood count: Hb. 12 gm.; R.B.C. 4,100,000; W.B.C. 8,000; polymorphonuclears, 54 per cent; lymphocytes, 46 per cent.

CASE 8.—N. J., C-7450, colored male, aged 11 months, weight nineteen pounds, was admitted Nov. 8, 1937 and discharged Nov. 16, 1937 (Table XI). The child's mother had a discharging eye two weeks before the patient was infected. The child had a very profuse discharge from both eyes which started three days prior to admission, with the lids markedly swollen and the conjunctivae chemotic. The cornea was negative. Smears were positive. Sulfanilamide was started promptly on admission. On the second day scanty discharge was present; on the fifth day both eyes were opened and the discharge had ceased; the conjunctivae approached a normal state. On the seventh day three negative smears were obtained, and sulfanilamide was discontinued. The patient was seen on Nov. 19, 1937, and on Nov. 26, 1937, with no recurrence; Kahn test, negative.

CASE 9.—A. J., C-7465, colored male, aged 3 years, weight 44 pounds, was admitted Nov. 11, 1937 and discharged Nov. 19, 1937 (Table XII). (This patient is a brother of No. C-7450.) On the evening prior to admission reddening of the left eye was noted. By morning the eye was swollen shut and pus was oozing between the lids. On admission chemosis was marked and symptoms of general constitutional involvement were present. Sulfanilamide was started promptly, and within two days there was considerable reduction in the local reaction and the discharge. Discharge continued, however, until the sixth day, at which time the left eye was open. By the ninth day all conjunctival involvement had subsided; Kahn test, negative.

TABLE XII

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
11/11*	–	+	–	++++	20 gr.	
11/12	–	–	–	+++	40 gr.	
11/13	–	–	–	+++	40 gr.	3.5 mg.
11/14	–	–	–	+	40 gr.	
11/15	–	–	–	+	40 gr.	
11/16	–	–	–	–	40 gr.	
11/17	–	–	–	–	40 gr.	5.8 mg.
11/18	–	–	–	–	40 gr.	
11/19†	–	–	–	–	40 gr.	

*Blood count: Hb. 13 gm.; R.B.C. 3,620,000; W.B.C. 15,700; polymorphonuclears, 84 per cent; lymphocytes, 12 per cent; monocytes, 3 per cent; eosinophiles, 1 per cent.

†Blood count: Hb. 13.2 gm.; R.B.C. 4,350,000; W.B.C. 7,900; polymorphonuclears, 55 per cent; small lymphocytes, 26 per cent; large lymphocytes, 18 per cent; eosinophiles, 1 per cent.

CASE 10.—D. B., C-7548, white male, aged 10 days, weight 4¾ pounds, was admitted Nov. 14, 1937 and discharged Nov. 19, 1937 (Table XIII). Discharge was noted on the fourth day after birth, involving the left eye. The mother had a profuse, purulent discharge during the last few months of pregnancy. She was treated by the family physician, and at delivery Credé prophylaxis was used. Two smears taken at home were positive for Neisserian infection. The child was admitted to the hospital showing puffy edematous lids of the left eye with a moderate yellow, purulent discharge. The conjunctiva was thickened and injected; no corneal involvement was noted. The right eye appeared negative. After obtaining positive smears, sulfanilamide was started. By the fifth day the discharge had entirely ceased. The eyes were opened and the conjunctiva appeared normal. The child was seen subsequent to discharge on March 2, 1938, and March 5, 1938, and smears taken at that time were negative; Kahn test, negative.

TABLE XIII

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
11/14*	–	+	–	++	5 gr.	
11/15	–	+	–	++	5 gr.	
11/16	–	–	–	++	5 gr.	
11/17	–	–	–	+	5 gr.	3.2 mg.
11/18	–	–	–	–	5 gr.	
11/19†	–	–	–	–	5 gr.	

*Blood count: Hb. 14 gm.; R.B.C. 4,800,000; W.B.C. 17,000; polymorphonuclears, 42 per cent; lymphocytes, 58 per cent.

†Blood count: Hb. 12 gm.; R.B.C. 4,530,000; W.B.C. 9,900; polymorphonuclears, 57 per cent; lymphocytes, 42 per cent; eosinophiles, 1 per cent.

CASE 11.—W. H., C-7817, colored male, aged 7 days, weight 3¾ pounds, was admitted Nov. 18, 1937 and discharged Dec. 4, 1937 (Table XIV). This child was a seven-month premature baby, born at home; Credé prophylaxis was used. Discharge started on the second day after birth with considerable chemosis of both eyes. The mother gave a history of a vaginal discharge during the last four months of pregnancy. Eye smears were positive, and the patient was admitted to the hospital. Hemolytic jaundice of the newborn infant was present. The child was placed on sulfanilamide, and by the third day discharge had become scanty. On the fifth day both eyes were open, discharge had ceased, and the smears were negative. The child was transferred to the premature ward and kept in the hospital until he had attained a weight of 5 pounds. He was seen in the out-patient department on Feb. 14, 1938, and Feb. 16, 1938, at which time the eyes appeared normal. Kahn test was negative.

TABLE XIV

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
11/18*	+	+	+++	++	2½ gr.	
11/19	–	–	+	+	5 gr.	
11/20	–	–	–	–	5 gr.	3.5 mg.
11/21	–	–	–	–	5 gr.	
11/22	–	–	–	–	5 gr.	
11/23	–	–	–	–		
11/24†	–	–	–	–		

*Blood count: Hb. 16.7 gm.; R.B.C. 3,800,000; W.B.C. 7,600; polymorphonuclears, 60 per cent; lymphocytes, 38 per cent; eosinophiles, 2 per cent.

†Blood count: Hb. 15.8 gm.; R.B.C. 3,600,000; W.B.C. 7,500; polymorphonuclears, 61 per cent; lymphocytes, 36 per cent; monocytes, 2 per cent; eosinophiles, 1 per cent.

CASE 12.—W. T., C-7972, white male, aged 5 days, weight 5 pounds, was admitted Nov. 30, 1937 and discharged Dec. 7, 1937 (Table XV). This child's left eye became involved on the third day after birth, with discharge and swelling of the lids. Credé prophylaxis was used at birth. The father had been treated at Receiving Hospital six months previously for a urethral stricture. On admission there was a thick, yellow discharge from the left eye; the conjunctiva was involved, the cornea was clear. Sulfanilamide was started promptly, and by the fourth day discharge had ceased. Conjunctival thickening had resolved. The smears were negative. The child was seen one week after discharge from the hospital, at which time the eyes were clear; Kahn, negative.

TABLE XV

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
11/30	–	+	–	++	5 gr.	
12/1	–	+	–	++	5 gr.	
12/2	–	–	–	+	5 gr.	
12/3	–	–	–	–	5 gr.	3.1 mg.
12/4	–	–	–	–	5 gr.	
12/5	–	–	–	–	5 gr.	
12/6*	–	–	–	–	5 gr.	
12/7	–	–	–	–		

*Blood count: Hb. 17.5 gm.; R.B.C. 4,200,000; W.B.C. 10,100; polymorphonuclears, 42 per cent; lymphocytes, 52 per cent; monocytes, 1 per cent; eosinophiles, 5 per cent.

Blood count, Dec. 21, 1937: Hb. 17.6 gm.; R.B.C. 4,560,000; W.B.C. 13,100; polymorphonuclears, 49 per cent; lymphocytes, 41 per cent; monocytes, 2 per cent; eosinophiles, 7 per cent; basophiles, 1 per cent.

CASE 13.—J. D., C-8385, colored female, aged 12 days, weight 4 pounds, was admitted Dec. 15, 1937 and was discharged Jan. 10, 1938 (Table XVI). The child was born at home, 7 months premature; Credé prophylaxis used: mother had a positive Neisserian history and had received prenatal care. Both eyes were involved three days prior to admission. Smears were positive. Lids were edematous and tumefied; the conjunctivae were thickened and protruded through the lids. The corneas were clear. Sulfanilamide was started, and by the fourth day both eyes were open, discharge had ceased, and the smears were negative. The child was kept in the hospital until it had reached the weight of 5 pounds. She was seen in the out-patient department, at which time the eyes were negative. Kahn test was negative.

TABLE XVI

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
12/15	+	+	+	++	2½ gr.	
12/16*	–	–	–	+	5 gr.	
12/17	–	–	–	+	5 gr.	3.6 mg.
12/18	–	–	–	–	5 gr.	
12/19	–	–	–	–	5 gr.	
12/20	–	–	–	–	5 gr.	

*Blood count: Hb. 15 gm.; R.B.C. 5,390,000; W.B.C. 13,400; polymorphonuclears, 60 per cent; small lymphocytes, 36 per cent; large lymphocytes, 4 per cent.

Blood count, Dec. 27, 1937: Hb. 15.5 gm.; R.B.C. 5,000,000; W.B.C. 16,800; polymorphonuclears, 54 per cent; lymphocytes, 44 per cent; basophiles, 1 per cent; eosinophiles, 1 per cent.

Blood count, Feb. 7, 1938: Hb. 7.5 gm.; R.B.C. 2,600,000; W.B.C. 5,500; polymorphonuclears, 52 per cent; small lymphocytes, 20 per cent; large lymphocytes, 20 per cent; eosinophiles, 8 per cent.

CASE 14.—M. W., C-8425, white female, aged 12 days, weight 6½ pounds, was admitted Dec. 21, 1937 and was discharged Dec. 25, 1937 (Table XVII). The child was born at Grace Hospital and received Credé prophylaxis. She was discharged for home on the fifth day. The following day the left eye began to swell and a copious, yellow discharge began and persisted until admission to the hospital. There was no corneal involvement on examination; there was moderate swelling of the lids of the left eye, and tumefied, moderate involvement of the conjunctiva was noted. Smears were positive, and sulfanilamide was started. By the fifth day the discharge had ceased entirely. The eye was open and the conjunctiva less involved. Patient was seen on Jan. 1, 1938, at which time there was no involvement noted. Kahn test was negative.

TABLE XVII

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
12/21	–	+	–	++	2½ gr.	
12/22*	–	–	–	+	5 gr.	
12/23	–	–	–	–	5 gr.	2.5 mg.
12/24	–	–	–	–	5 gr.	
12/25	–	–	–	–	2½ gr.	

*Blood count: Hb. 17 gm.; R.B.C. 4,500,000; W.B.C. 18,200; polymorphonuclears, 44 per cent; lymphocytes, 56 per cent.

CASE 15.—A. B., A-3537, colored female, aged 3 weeks, weight 9 pounds, was admitted Jan. 1, 1938 and discharged Jan. 5, 1938 (Table XVIII). This child was born at home and was referred by the Board of Health with a discharging right eye which began shortly after birth. On admission smears were positive from both eyes, and moderate palpebral conjunctival involvement was present. There was slight discharge from both eyes. No corneal ulceration was present. Sulfanilamide was started, and by the fourth day complete resolution with negative smears and normal appearing conjunctivae were present. Patient was seen on Jan. 25, 1938, and the eyes were negative; Kahn, negative.

TABLE XVIII

DAYS	SMEARS		DISCHARGE		SULF.	SULF. LEVEL
	RIGHT EYE	LEFT EYE	RIGHT EYE	LEFT EYE		
1/1	+	+	+	+	2½ gr.	
1/2*	–	–	–	–	5 gr.	
1/3	–	–	–	–	5 gr.	
1/4	–	–	–	–	5 gr.	2.1 mg.
1/5	–	–	–	–		

*Blood count: Hb. 13 gm.; R.B.C. 4,600,000; W.B.C. 7,600; polymorphonuclears, 67 per cent; small lymphocytes, 28 per cent; large lymphocytes, 5 per cent.

SUMMARY

The most satisfying observation in the use of sulfanilamide in the treatment of gonococcic ophthalmia was the rapid decrease in the swelling and discharge. Patients with red, chemotic, bulbar conjunctivae, with swollen retrotarsal folds and tumefied lids showed a uniformly prompt subsidence. Since this type of case is more apt to have implication of the cornea, if untreated, the rapid arrest noted with sulfanilamide is responsible, we believe, for a much better prognosis.

In conclusion, we have observed a reduction of hospitalization of from 28.5 days for a control series of thirty-two patients with gonorrheal ophthalmia to 5.8 days for a series of fifteen patients treated with sulfanilamide. We believe the use of sulfanilamide is warranted in the treatment of gonorrheal ophthalmia for the following reasons: (1) economic importance, sharply reducing the length of hospitalization; (2) the ease of administration; (3) the apparent lack of complications; (4) the rapid improvement found; and (5) the general increase in the comfort of the patient.

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RUPTURE OF THE LIVER IN THE NEWBORN INFANT

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ALTHOUGH vascular abnormalities of the liver are by no means rare, rupture of the liver with resulting death in the newborn infant is seldom reported. Hemangiomas, either small or of the large cavernous type, are very frequently described, although they rarely give rise to any symptoms in the newborn period. Small subcapsular hemorrhages are frequently met with on the autopsy table, but actual damage to the liver structure is very rarely seen. Apart from the rare reports of cases of liver rupture due to direct trauma, rupture of the liver occurs as a cause of death in a small group of the newborn infants. The etiology of this condition is inadequately explained.

Before 1917, when Hedren compiled the literature, it was felt that rupture of the liver was not possible in spontaneous labor. Since that time, however, Pim and Barlow described one case in 1932, and McNitt described two cases in the same year. In 1933 Henry S. Meyer described another case. In 1936 Schmitt described three cases, only one of which, however, occurred in spontaneous delivery. Although in stillbirths injury to the liver is very frequently demonstrated, it is rare in children born alive. All of these cases reported were in living children.

The liver of the newborn child averages about 4 per cent of the total body weight of the newborn child. It is normally palpable, about 2 to 3 cm. below the free costal margin. As the child lies in the uterus in the fetal position, the liver is at what may readily be conceived of as a point of maximum pressure. It is the keystone of an arch, formed by the back of a child, against which the legs and feet are pressed when the tremendous forces incident to active labor occur. When it is remembered how forcible the uterine contraction is and how exposed to injury this large, soft organ seems to be, it is surprising that injury occurs as infrequently as it does. Due to the protective capsule about the liver, unless the lacerations are extreme, immediate severe bleeding does not occur. What actually happens is that a slow, continuous hemorrhage from the lacerated liver tissue lifts the capsule and causes a subcapsular hematoma. Ordinarily the pressure upon this hematoma within the capsule controls the bleeding. In occasional cases, however, where the injury is severe enough, the bleeding continues until the pressure within the hematoma has risen to a point where the capsule is ruptured and free blood is poured into the abdomen. This produces the characteristic clinical history of the condition.

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The child is born apparently normal and with only moderate evidence of birth shock. It seems perfectly well until about the third or fourth day, when it suddenly goes into collapse and dies. Occasionally, as occurred in our case, some of the characteristic symptoms of free intra-abdominal bleeding are present. There is a doughy feel of the abdomen and a discoloration either about the umbilicus or along the inguinal gutter and the scrotum. Aspiration of the abdomen may reveal free blood. On the autopsy table the tear in a capsule is readily seen. There is ordinarily no definite tear of the liver structure, although the adherent blood clot of the subcapsular hematoma gives direct evidence of the injury to the liver itself.

In going over the literature I have been able to find four other cases reported that appear in their clinical manifestations to be of the same type as the case that we are reporting.

Pim and Barlow[1] report the following case:

A primipara was delivered of a male infant weighing 10 pounds 14 ounces. The labor lasted about twenty-three hours, the presentation being left occipitoanterior, and terminated naturally, but with considerable laceration of the perineum. The infant started to breathe shortly after the head was born. There was a good deal of delay in the birth of the shoulders, and toward the latter part of this delay breathing ceased, and some cyanosis became apparent. After the birth of the shoulders, breathing restarted with slight stimulation. Neither Schultze swinging nor compression of the chest was used.

The child was well-formed and apparently quite healthy. On the second and third days it seemed quite well and was fed from the breast. On the fourth morning it was observed that it was slightly jaundiced, but otherwise well. In the afternoon the nurse noticed that the child seemed weak and listless, and from that time the weakness increased, until at 6 A.M. on the fifth day the baby collapsed and died.

Post-Mortem Examination.—When the peritoneum was opened, it was found to be full of dark liquid blood. All the organs appeared normal except the liver. On the outer surface of the right lobe was a hematoma, the size of half a billiard ball, full of diffluent blood, and about the center of the hematoma there was a linear tear ½ inch long in the capsule of the liver, through which blood was leaking. Around the edges of the tear was a small, soft clot.

McNitt[2] reported the following two cases:

A multipara, aged 29 years, had three previous full-term labors with two forceps deliveries. One day before the estimated date of confinement the patient went into labor. At this time the position was R.O.P., and the fetal heart was strong. After six hours of hard labor with the cervix practically dilated, the position was still R.O.P. The abdomen was manipulated between pains, with the end in view of turning the fetus. This was accomplished quite easily, and about twenty minutes later a baby boy, weighing 8 pounds, was born.

The child took the breast well and appeared perfectly normal. Two days later the baby suddenly vomited, its respiration became more rapid, and its skin became anemic in appearance. One hour later it died. Artificial respiration failed, as did intracardiac injections of adrenalin.

Autopsy Report.—On opening the abdomen many large clots of blood were seen. A large clot was noted more firmly attached to the under surface of the liver. On close examination, a rent in Glisson's capsule, approximately 1 inch in length, was

found, and beneath this, a corresponding laceration of the liver substance. This tear extended from a point on the inferior surface of the right lobe near the vertebrae, laterally, and forward for the distance of 1 inch. A clot was firmly attached to the bed of the laceration. All organs were anemic in appearance. The tentorium cerebelli showed no laceration or hemorrhage.

A white multipara, aged 23 years, in a previous pregnancy had twins who died when 3 days old. The cause was unknown, and there was no autopsy. On Oct. 31, 1930, the patient went into labor at 4:30 A.M.; the membranes ruptured at 4:00 P.M., and birth of a male infant weighing 9 pounds 3 ounces took place at 7:35 P.M. on the same day. The position was L.O.A. Ether anesthesia was used and there was a loop of cord around the infant's neck. Three days later, on November 3 at 4:30 P.M., the baby apparently became very hungry (thirsty?), regurgitated, grew pale, defied all attempts at resuscitation, and died at 12:30 A.M. The child's temperature ranged from 99° F. to 101.8° F.

At the end of the second stage of labor, mild pressure was exerted on the abdomen during pains in order to assist the slow descent of the large child through the birth canal. This was the only antepartum manipulation made.

Autopsy Report.—There was an intra-abdominal hemorrhage of dark thick blood. A large clot was found toward the posterior inferior aspect of the right lobe beneath the capsule of Glisson, filling the proximal portion of the right lateral gutter. Dissecting the capsule of Glisson, almost over the entire postinferior aspect of the right lobe, the subcapsular hemorrhage measured 2½ inches by 1½ inches. On removal of the liver, a more or less elliptical slit or rupture was noted in the capsule, extending toward the lateral aspect of liver margin.

In both of these cases, extra-abdominal manipulation of the uterus was attempted, and the author felt that possibly this manipulation was the cause of the rupture.

In 1933 Henry S. Meyer[3] reported the following case:

L. S., a white male, was delivered July 8, 1933. The labor was hard and of eight hours' duration. The child was delivered by low forceps. A median episiotomy was done. The position was occipitoanterior. The child weighed 10 pounds at birth. There were no cyanosis, convulsions, paralysis, or malformations. The child apparently nursed well but continued to lose weight very rapidly during the first five days. On July 13 there was a sudden collapse, and a diagnosis was made of collapse, due to hemorrhage into one of the viscera.

Autopsy Report.—The abdomen, when opened, revealed about 500 c.c. of sanguineous fluid. The capsule of the liver showed a rent about 3 cm. long. It had been dissected from the anteroinferior surface of the right lobe and part of the left lobe. The liver was spongy over the entire area.

Author's case:

The mother was a 24-year-old primipara. The entire pregnancy had been normal. She entered the hospital in labor at 4:15 P.M., on Jan. 11, 1936, and delivered spontaneously at 8:28 the same day. Labor was short, no medication was used; episiotomy was done, and gas-oxygen anesthesia was employed. The mother's condition was normal and remained so throughout the post-mortem period. Kahn and Wassermann tests were all negative for father, mother, and child.

The child, born at 8:28 P.M., Jan. 11, 1936, weighed 7 pounds 2 ounces. There was normal spontaneous delivery. No anomalies or cyanosis were noted. The child began to cry immediately and for the first twenty-four hours seemed to be perfectly normal. At 9:15 P.M. on the following day, Jan. 12, the nurse noted that the scrotum and right inguinal region were edematous and cyanotic. The extremities were cold,

and the baby appeared to be in shock. At 1:10 A.M., Jan. 13, the baby was seen. The right inguinal region and right scrotum were definitely ecchymotic, and the baby still appeared to be in shock. Temperature was subnormal, pulse very rapid, and abdomen weak. Paracentesis was done, and 5 c.c. of liquid blood was obtained. Diagnosis of a ruptured viscus was made, and the child was treated for shock. By 10:30 A.M., Jan. 13, there was marked edema of the scrotum with increasing ecchymosis. The discoloration was sharply defined and extended upward along the right inguinal region. The abdomen was distended and had a doughy feel. There was no blood in the stools or vomit. The child died within about three hours.

Autopsy Report.—The body was that of a 2-day-old white, male infant. Rigor mortis was absent. There was no jaundice, edema, or petechiae. The abdomen appeared unusually distended. Just below and to the left of the umbilical scar, which was well-healed, there was a pinhead-sized dark red zone, the site of a recent paracentesis. The right scrotal sac appeared purple in color and felt tense on palpation. The left scrotal sac was less markedly discolored. Both testes were in the scrotum. There was no external anomaly.

Internal Examination.—On opening into the abdominal cavity, a gush of fluid blood resulted. The whole abdominal cavity was filled to distention with a considerable quantity of dark red fluid blood, which enveloped all the intra-abdominal viscera, but was most pronounced in the right lumbar gutter. The under surface of the right lobe of the liver presented a circumscribed area about 2 cm. in diameter consisting of a collection of semifluid and coagulated blood lying beneath the capsule. The latter was intact except at one point where a ragged rent was visible, from which a moderately firm, grayish-red, friable cylindric blood clot extended down into the right lumbar gutter. The remainder of the liver appeared intact.

The lungs were pinkish in color, soft, and crepitant.

The heart presented no abnormalities. The foramen ovale was represented by a crescentic opening. The kidneys showed fetal lobulations. The capsules stripped readily, leaving a smooth surface. Cut section showed the usual cortical and medullary structure. Pelves, ureters, and bladder were negative.

The scrotal sac was distended and discolored to a dark red color. The right processus vaginalis was found to contain a large collection of fluid and partially coagulated blood which surrounded and compressed the testis, which appeared normal.

The diagnosis was subcapsular hematoma of under surface of the right lobe of the liver, with rupture into peritoneal cavity and resultant hemoperitoneum.

DISCUSSION

The etiology of the rupture of the liver in the newborn infant is difficult to explain. A number of theories have been advanced. McNitt felt that the possibility of abdominal ante-partum manipulations, utilized in attempting to change the position of the fetus before delivery, may have been the distinctive factor in his cases. It is conceivable that with the application of pressure binders the normal forces of the uterine contractions may be so distorted that forcible pains acting against a brace, supplied by the abdominal binding, might conceivably injure the liver. However, there is really no direct evidence for this. In our own case, no such ante-partum manipulation was done.

In a case of Pim and Barlow, the difficulties of the labor itself may have been a factor in the injury. The twisting of the body, incidental to the difficult delivery of the shoulders, could possibly have put the

liver in a more exposed position. In the other cases, however, those of Meyer and our own, labor was practically normal. It would seem that some abnormality of either the position of the fetus or of the stresses of labor would be necessary to cause the rupture. In addition, it may also be essential that some underlying congenital anomaly exists.

Another possibility has been discussed at some length by Schmitt, who believes that mechanic-traumatic asphyxia should be considered as one of the etiological factors. The abnormally increased tendency to hemorrhage, the so-called pseudohemophilia, indicates a constitutional cause. The inability to demonstrate on the autopsy table actual laceration of the liver structure is in all probability dependent on the structure of the liver itself. Injuries of sufficient magnitude to cause tremendous bleeding in such a spongy organ may still present disintegration of the liver structure rather than definite tearing.

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CONGENITAL ABSENCE OF TEETH

Absent Deciduous and Permanent Right and Left Central and Lateral Incisors and the Canines of the Lower Jaw

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THE congenital absence of teeth is an uncommon occurrence as judged from experience both in the dispensary and in private practice. It is for this reason that we are reporting a case of this type. The medical literature on this subject is very small. Only occasionally does one find a reference in the orthodontic literature.

The etiology must be sought in the embryologic development of the teeth. The endocrines, whose importance in development is appreciated, have also been incriminated. Syphilis is known to interfere with normal development often involving the teeth. In this condition absence of teeth is uncommon. Dwarfism and changes in contour of the teeth are the usual picture in syphilis.

The teeth are derived from both ectoderm and mesoderm. In human embryos, before the lip groove is formed, a thickening of surface ectoderm takes place along the edges of the processes that bound the slitlike entrance to the mouth. When the lip groove appears, the epithelial thickening comes to lie along the edge of the jaw, i.e., along the edge of the gums. This ridge grows into the mesoderm of the jaw, toward the lingual surface, and is now known as the dental shelf. This shelf is at first of uniform thickness throughout, but soon five enlargements appear in it in each upper and lower jaw, indicating the beginnings of the milk teeth. At the 40 mm. stage (eleven weeks), a condensation of mesenchymal tissue beside the deciduous teeth pushes its way into the enlargements of the dental shelf. These ingrowths are called dental papillae. The epithelium gives rise to the enamel organ and the dental papillae (mesoderm) give rise to the dentine and the pulp. These anlagen are connected to each other by dental shelf and to the surface by original ingrowth of ectoderm. Part of the dental shelf grows even further lingually, in which portion the beginnings of the permanent teeth arise. From the foregoing description, it is obvious that any interference with the surface ectoderm in this region, or the region of the dental shelf, may produce either partial or complete edentia.

Congenital absence of teeth may be familial, as pointed out by Pitts,[1] who reports the absence of both deciduous and permanent central incisors with absence of the permanent lateral incisors in two members of a family. The same author reports another case in which there was congenital absence of all teeth but two molars in the lone survivor of pre-

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mature twins. This patient had coarse, dry hair, suggesting also a faulty primitive ectoderm.

Bray,[2] in 1934, reported a case of complete edentia in an otherwise normal child. Another child in the same family had normal development in every respect. Gardner and Dillery[3] report a case in which twenty-three of the permanent teeth failed to develop.

The description of our case follows:

M. B., aged 4½ years, has been under the care of one of us (J. L. S.) since birth. The birth weight was 5 pounds and 6 ounces. The child was fed a modified cow's milk formula with the usual additions in the later months. Cod-liver oil and orange juice were given in sufficient quantity.

At birth the patient presented a right inguinal hernia. This had incarcerated on several occasions and required surgical intervention at the age of 3 months. Development was normal in all respects, with exception of the teeth. The mother's Wassermann test was negative, and there were no stigmas of congenital syphilis in the child. There were no other evidences of ectodermal or endocrinal defect.

The patient was referred to Dr. Glen H. Whitson for orthodontic examination and treatment. The following is his report:

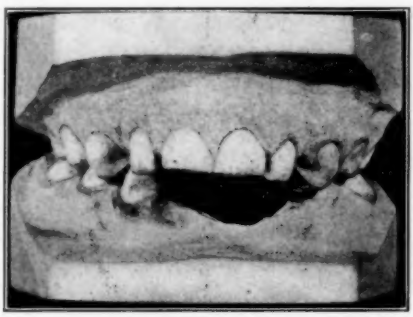

Fig. 1.

"Normal mesiodistal relationship of the upper and lower dental arches one to the other and to the cranium. The intercuspal relationship of the canine, first and second deciduous molars is normal. The upper deciduous incisors are protruding labially due to a tongue thrust habit. The lower left deciduous central and lateral incisors and the canine and the lower right deciduous central and lateral incisors and canine, six teeth in all, are missing. No history of a fall or blow which might account for the absence of these deciduous teeth.

"*Radiographic examination.*—The lower permanent right and left central and lateral incisors and the canines, six teeth in all, are apparently not present as there is no sign of their development. In the upper jaw all the permanent teeth are apparent, though the presence of the upper permanent canines at this age has not been definitely determined. In my personal experience, extending over twenty-five years, this is the first instance where the entire lower anterior deciduous dentition from left canine to right incisor is congenitally missing."

Treatment as suggested by Dr. Whitson is as follows:

"The all important objective right now for this boy is incisor function. This I believe can be established by making hard gold alloy cast overlay anchorage in combination for the first and second deciduous molars on the left side and cast overlays in combination for the deciduous canine and first molar on the right side.

Connect these anchorages with a heavy triangular shaped clasp metal bar so placed that it will function with the maxillary deciduous incisors. I feel justified in saying that such an appliance could remain in place until the four first permanent molars and maxillary central incisors are fully erupted. In addition to this, I would place an orthodontic appliance upon the upper teeth to restore the incisors in that jaw to their normal axial inclination and function."

A perusal of the scanty literature on this subject reveals no figures as to the frequency of this condition. The significance of absent teeth is obvious from both an esthetic and a nutritional viewpoint. Etiologically, the condition is related to developmental defect involving the primitive ectoderm of the oral region. A further possibility to be considered is

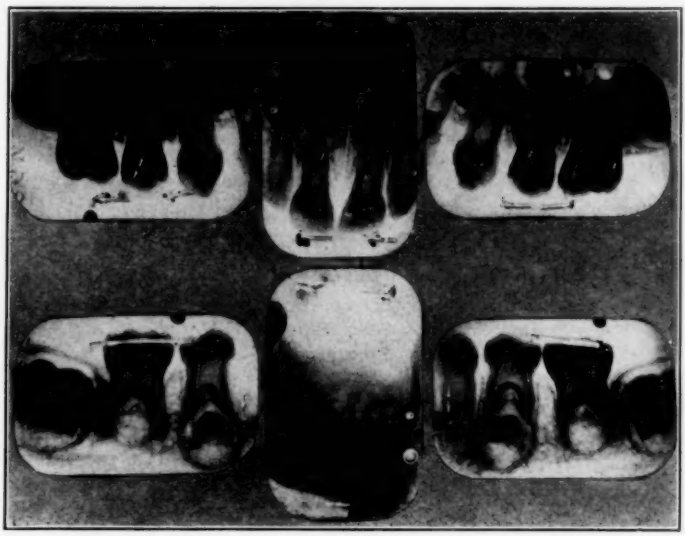

Fig. 2.

that of multiple defects in the ectodermal tissues related to defects in the primitive streak. Endocrinal disfunction and syphilis have been mentioned.

SUMMARY

The rarity of congenitally missing deciduous and permanent teeth is emphasized. A case is presented, a plan of treatment outlined, and the possible etiology suggested.

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METHYL SALICYLATE POISONING IN AN INFANT

Report of a Patient with Partial Necropsy

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ALTHOUGH methyl salicylate poisoning is a comparatively rare occurrence, especially in infancy, steps should be taken toward its prevention. When taken internally for therapeutic purposes symptoms of intoxication may occur; but the accidental or intentional taking of an overdose has been followed by a mortality in 59 per cent of the cases. Forty-one[1] per cent of the cases of poisonings occurred in infants. A review of the literature, from the case reported by Gallaher[2] in 1852 to the one reported by Stevenson in 1937, reveals a total of 47 cases.

The following case is of interest because of the severe intoxication and death that was produced from a dose of only one teaspoonful of synthetic oil of wintergreen, and because of the normal carbon-dioxide tension with clinical symptoms of a severe acidosis.

Case Report.—D. C., a boy aged 22 months, was sent into the Park City Hospital on the evening of Oct. 25, 1937, having swallowed one teaspoonful of oil of wintergreen at 8 o'clock that morning. Soon after, the child began to vomit, but the mother thought nothing of it. Vomiting increased and the child began to breathe rapidly and appeared quite drowsy. A physician was called and advised immediate hospitalization. At time of entrance the child had not retained any food or fluids for twelve hours and had become quite stuporous.

Physical Examination.—On admission the child appeared very ill; breathing was rapid and slightly labored. Soon after admission the respirations took on the Kussmaul type of breathing. The pupils were equal and regular but slightly contracted. The skin, lips, and tongue showed evidence of marked dehydration. The child was restless and craved for water, which was immediately vomited. The abdomen was soft. There were no abnormal neurological signs. The temperature on admission was 99° F., pulse rate, 110, and respiration rate 40. Blood pressure was 95 systolic, with a diastolic pressure of 60. The respirations became deeper and more labored, and there was an odor of oil of wintergreen on the breath, but no acetone could be detected. Immediate urinalysis showed only a slight trace of albumin and acetone. Microscopic examinations were negative. The Benedict reaction was negative.

Course in Hospital.—Shortly after admission the child was given an intravenous injection of 350 c.c. of 5 per cent glucose in a normal saline solution. Blood was taken for a carbon-dioxide tension and sugar determination. During the night the child had several clyses which were immediately absorbed because of the severe dehydration present. Since the carbon-dioxide tension was 57 volume per cent, and the blood sugar was normal, 112 mg. per 100 c.c., alkali treatment was not given, but a continuous intravenous infusion of 5 per cent glucose in a normal saline solution was started the following morning. The patient showed no response to these therapeutic measures, and his condition became steadily worse. A transfusion of 200 c.c. of whole blood was given by direct method. That evening

the child became cyanotic and was placed in an oxygen tent. During the day several urine specimens were obtained, which gave a positive Gerhardt test of a violet color for salicylates. Tests for acetone and diacetic acid were only slightly positive. Early the following morning the patient developed generalized convulsions. A lumbar puncture was performed, and the spinal fluid was normal in pressure and cell count. The spinal fluid gave a negative Gerhardt test for salicylates. Thirty-six hours after admission the child's condition became very poor, signs of pneumonia appeared, the temperature rose to 105° F., and pulse rate increased to 160. The child died.

Additional Laboratory Examinations.—The admission specimen of urine showed only slight trace of albumin and acetone, but no sugar. Subsequent urine examination showed traces of acetone and diacetic acid. Sugar continued to be negative. Microscopic examination of the urine was negative. A blood count taken on admission showed: red blood cells, 4,300,000; hemoglobin, 65 per cent (Sahli); white blood cells 18,500; polymorphonuclears, 47 per cent; lymphocytes, 53 per cent. The red cells appeared normal on the smear.

Autopsy.—There were no scars or deformities present. Rigor mortis was weak, and post-mortem settling was slight. The eyes were sunken and the pupils moderately dilated and equal.
On section, the body showed the following:

Abdomen: no abnormalities.
Right and left pleural cavities: no abnormalities.
Pericardial sac: no abnormalities.
Heart: the myocardium was friable and pale; the endocardium and its valvular leaflets were normal.
Lungs: slight pulmonary edema.
Liver: the capsule was smooth; the parenchyma on section showed considerable fatty infiltration.
Gall bladder and bile ducts: normal.
Spleen: normal.
Pancreas: normal.
Gastrointestinal tract: normal.
Kidneys: the capsule stripped readily; the parenchyma was pale and bulged from beneath the capsule.
Pelvis, ureters, and bladder: normal.

Anatomic Findings:

Pulmonary edema.
Cloudy swelling of all the parenchymatous organs.
Fatty infiltration of the liver.

Microscopic Examination:

Liver: marked fatty degeneration of the liver cells.
Spleen: no changes.
Kidney: marked congestion with a swollen granulated appearance of the convoluted tubules; there was marked irregularity in the size of the glomeruli.
Lungs: moderate degree of congestion of the septal vessels.

Heart muscle: cells had cross striations and presented a hyaline appearance.

Histological findings:

Nephrosis, of kidney.
Cloudy swelling and albuminous degeneration of the heart muscle.
Fatty degeneration of the liver.
Congestion of the lungs.

DISCUSSION

In reviewing the literature on methyl salicylate poisoning, the amount of methyl salicylate swallowed in the fatal cases varied from 4 c.c. to 15 c.c. The smallest recorded lethal dose was reported by Hughes,[3] in a male infant who was given 4 c.c. of synthetic oil of wintergreen by mistake. However, recovery has occurred in cases in which the dose was considerably in excess of this. Meyers[4] reported a case in a child, 2 years of age, who swallowed 30 c.c. and recovered.

The intimate relationship of the salicylates to the phenols and their possible toxic properties was stated by Wetzel and Nourse[5] in 1926. Of the salicylates, the methyl ester is much more respected, therefore, the sodium salt is more frequently used in treatment. The toxicity of methyl salicylate, according to Hanzlik and Wetzel,[6] is said to be due, in part, to the greater lipoidal solubility and, in part, to the fact that it suffers less destruction within the body after absorption.

The symptomatology and physical observations in the cases previously reported are similar in many respects. My case presents many of the clinical features reported in those cases. The symptoms can be grouped under three classes, namely: gastrointestinal, respiratory, and central. The gastrointestinal symptoms are due to the direct irritant action of the drug on the mucosa of the stomach and intestines. Some cases presented few, if any, outstanding symptoms. Vomiting and diarrhea are constant features. Woodbury and Nicholls[7] reported two cases: in one, the only symptom was vomiting; in the other, there were vomiting and convulsions. In my case, the vomiting occurred early and persisted for twenty hours, although it was never bloody. The cerebral symptoms are prominent in the severe cases. These symptoms such as marked irritability, increasing stuporousness, mental dullness, and generalized convulsions were very prominent in my case. The causation of the cerebral symptoms is less obvious, and some of the symptoms such as deafness and disturbance of vision are known to accompany salicylate poisoning.[8] The most spectacular symptom, the hyperpnea, seen also in my case, seems to be the most widely discussed. Because of the Kussmaul type of breathing, it was thought to be caused by an acidosis, since most investigators agree that there is some reduction in the carbon-dioxide capacity of the blood plasma in salicylate poisoning. Johnson[9]

found that in four of his eight experimental cats which had received the equivalent of a full therapeutic dose of sodium salicylate there was a significant decrease on the alkali reserve and that in these four there was an increase in blood lactates. Hanzlik,[10] on the other hand, does not consider the reaction of air hunger in salicylate poisoning to be of the nature of an acidosis because he did not find any shift in the hydrogen-ion concentration. Veil and Graubner,[11] Gebert,[12] and Odin[13] suggest that the salicylates have an irritative action on the respiratory center, which produces hyperventilation. This in turn causes a decreased carbon-dioxide content of alveolar air and blood and a reduction of fixed alkali in the blood by excretion of an alkaline urine. For this reason they believe alkali treatment is contraindicated in salicylate poisoning. Morris and Graham,[14] on the other hand, state that the air hunger in salicylate poisoning cases was due to a nongaseous acidosis, and because of the acidosis and impairment of renal function, they believe the only form of treatment is by alkalies and not glucose.

Although many cases of salicylate poisoning have been reported and their similarity to diabetic coma noted, few authors have determined the actual existence of a severe acidosis by means of a carbon-dioxide combining power of the blood plasma. Longmead[15] in 1906 reported eight cases of salicylate poisoning in children and called attention to the similarity of these cases to diabetic acidosis. In 1936, Bowen, Roufa and Clinger[16] reported a case of methyl salicylate poisoning in a child eighteen months of age and noted in their patient the similarity of salicylate poisoning to diabetic coma. The carbon-dioxide capacity was found to be 50 volumes per cent. These authors believe the symptoms resembling diabetic coma to be one of an irritative action on the respiratory center, rather than a true acidosis. Pincus and Handley,[17] on the other hand, in their case found the carbon-dioxide combining power to be 36 volumes per cent. Olmstead and Aldrich[18] reported two cases, and their determinations were 33.5 per cent and 37.6 per cent. Dwyer,[19] in 1933, reported one case of 36.5 per cent. In my case the findings of the carbon-dioxide combining power were 57 volumes per cent. Because of this normal value, the child was treated with intravenous saline solutions and 5 per cent glucose. Most investigators agree that the ideal treatment of salicylate poisoning is large amounts of alkalies, both by mouth and rectum, and intravenously in the more severe cases. Nevertheless, every patient suspected of any salicylate poisoning should have a carbon-dioxide combining power done before alkali therapy is started.

While a number of cases were studied at necropsy, the pathologic conditions described seem to show certain changes which were found in my case. In 1928 Woodbury and Nicholls described an acute gastritis, congestion and edema of the lungs, and acute degenerative parenchymatous nephritis. Wetzel and Nourse found hemorrhagic areas in the lungs; the liver showed generalized fatty changes and cloudy

swelling; with cloudy swelling and fatty degeneration of tubular portion of the renal cortex. Meyerhoff[20] reported changes of an early glomerular nephritis; cloudy swelling and fatty degeneration of the liver.

SUMMARY

1. Four cubic centimeters of methyl salicylate can produce death in infants. Methyl salicylate should be dispensed with proper warning as to its possible dangers when taken internally, and since the drug is used so freely, steps should be taken toward its prevention.

2. The clinical and pathologic findings in this case are similar to those previously reported.

3. When dealing with a case of coma, salicylate poisoning should be considered, and if possible a carbon-dioxide combining power should be done so as to determine whether to give alkali therapy or not.

4. Since most cases that have been reported show a low carbon-dioxide combining power, the therapy of choice would be some form of alkalies, either by mouth or intravenously if the case is severe.

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Critical Review

HEREDITY IN DISEASE

A Review of the Recent Literature

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THE increasing recognition of the importance of genetic factors in disease warrants a detailed study of the recent literature on this subject. There are available several reviews of heredity which give general summaries of the subject.[1, 2] The purpose of this article is not merely to catalogue the work done by various authors, but rather to present a critical survey of the past year in order to emphasize the recent trends in this field.

There are three important fields in which genetic data find application. There is, first, the immediate clinical significance to the physician in the care of a given case. Second, there is the application of the data of human heredity to eugenic problems. This is a very controversial field which we shall touch upon but briefly. Third, there is the application of the data to political and economic problems about which, unfortunately, a great deal of harmful and vicious misinformation has been promulgated. We shall not touch upon this interesting aspect of the subject, which includes the consideration of race biology, but refer the reader to a recent book by J. B. S. Haldane.[3] This review will be limited for the most part to articles of clinical significance.

Material for the study of human heredity is so scarce that in this more than any other field of medicine are communal interests of different workers indicated. The isolated case reported by one author assumes increased significance when similar observations by another worker add to the statistical validity of the material.

It will not be possible in this review to consider the basic biologic material, the understanding of which is essential for any discussion on heredity. Such material, written especially with the view to its application to human problems, is available in a number of excellent books on the subject.[4]

The authors of this review have attempted as thorough a search of the literature as possible within the limits discussed above. There is no doubt, however, that a considerable number of articles have been missed, especially because so often genetic data are buried in articles in which the whole emphasis is either clinical or pathologic.

INTERNAL MEDICINE AND PEDIATRICS

Allergy.—The importance of heredity in development of allergic diseases has long been recognized and accepted. The questioning of this conclusion by Ratner[5] is surprising. His report, unfortunately, is in abstract form and the author himself apologizes for the generalities

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of his data. Ratner analyzes the family background of 250 allergic children and finds among them an incidence of allergy no greater than that in the general population. Wiener[6] and his colleagues present a more valid study of inheritance in allergic disease. They sought also for evidence of linkage with eye color and the blood group properties A, B, M, and N.[7] They distinguish, among patients with asthma, two types: the one with onset before puberty, the other with onset in the third decade of life. They postulate, instead of the accepted Mendelian mechanism which is that of simple dominant heredity, the existence of two allelomorphs, H and h. Individuals having the genetic composition HH are normal. Those with hh are asthmatics presenting the early type of the disease, while those with the heterozygous composition Hh either have the disease late in life or not at all. The authors did not find any evidence of linkage between allergic diseases and genes determining the blood group properties and eye color.

Digestive Diseases.—Körner[8] studied fifty-seven families of individuals who had been operated upon for gall bladder disease. He found an increased incidence of gall bladder disease in the families of 47.3 per cent of the patients. In these families there was also an increased incidence of diseases, considered by the author to be related to gall bladder disease, such as appendicitis, peptic ulcer, adiposity, and gout. In fifty-seven control families only two presented an increased incidence of the disease itself, and thirty-three families in this group had members who suffered from the so-called associated diseases. The author emphasizes that increased frequency of incidence of disease in a family is not necessarily the same as heredity, and the extrinsic factors in the causation of gall bladder disease must not be minimized.

Necheles and Levitsky,[9] in a study of the relation of constitution to peptic ulcer, conclude that ulcer patients secrete less saliva following pilocarpine than do normal individuals. In a previous article the same authors concluded that the apparently healthy members of the families of ulcer patients suffered from a similar type of pharmacodynamic abnormality.

The incidence of appendicitis in two families was compared with that computed for the general population by Baker.[10] Although the pedigrees are interesting and suggestive, the statistical work-up does not appear to be very reliable.

Sheldon[11] reports a case of hypertrophic pyloric stenosis in one of a set of uniovular twins. He reviews the literature on the subject, emphasizing that his experience is different from that of most other reports, in which usually both of the twins, when identical, are afflicted.

Cardiac Diseases.—Hecht and Gupta[12] studied the electrocardiograms of twins and concluded that the similarity of the tracings in identical twins is striking as compared to the lesser degree of similarity in ordinary twins.

A paper of unusual excellence is one by Wilson and Schweitzer[13] on rheumatic fever. This paper is important not alone for the material presented and the conclusions drawn, but also as an example of a careful, valid, statistical analysis. The authors emphasize the increased familial incidence of rheumatic fever, which is reported to be from 15 to 58 per cent. They consider three factors to be responsible. First, home environmental conditions; second, communicability; and third, susceptibility, probably on a hereditary basis. By an analysis of the relative

significance of these factors, the authors believe that hereditary susceptibility would seem to determine the familial incidence of rheumatic fever. They conclude: "It is reasonable to suppose that the acquisition of rheumatic fever may be dependent on the exposure of the susceptible individual to an etiological agent that is widespread in this geographical environment."

Ayman,[14] in a study of 1,524 persons in 277 families, ascribes a tendency to hypertension in early life to a hereditary basis. He states that so-called emotional hypertension occurs almost wholly in the young members of hypertensive families. However, he carries his conclusions too far in assuming the existence of a "special personality" in these hypertensive individuals, and the assumption that there is a heredity of personality demonstrable in his data.

Ullrich[15] describes a most unusual study of a set of triplets, all boys, two of whom were identical. These two presented congenital cardiac hypertrophy with fibrosis of the endocardium. The pathologic studies of the two abnormal children are included.

Infectious Diseases.—The study of heredity in relation to infectious diseases presents many difficult problems. Lehmann,[16] in a brief general discussion, assumes the existence of hereditary differences determining susceptibility to infectious diseases in human beings. An excellent summary of experimental studies of this subject on animals is presented by Hill[17] in which the available literature is subjected to a critical survey. The author points out the difficulty of eliminating the environmental factors concerned, particularly that of acquired immunity transmitted from infected ancestors. It was demonstrable, however, that between strains of the same species, differences in mortality from specific infections existed, which could be ascribed to differences in genetic composition.

Hofmeier[18] summarizes recent literature on the relation of heredity to immunity in human beings. He emphasizes the importance of studies in twins.

Metabolic Diseases.—Two papers on heredity of brittle bones and blue sclerae describe the usual dominant type of heredity that has previously been worked out in this disease. Burch and Sodeman[19] found forty-one afflicted individuals among seventy-six persons in five generations. Hills and McLanahan[20] found the condition in twenty-seven out of fifty-one persons in five generations.

Harnapp[21] describes the occurrence of a form of osteosclerosis in a father, two brothers, and three sisters. This condition is usually considered to be nonhereditary.

HEMATOLOGY

Hemophilia.—The heredity of hemophilia has long served as an exquisite example of heredity in the human being, demonstrating the Mendelian mechanism of recessive sex-linkage. Fonio,[22] who has reviewed the entire subject of hemophilia in an extensive monograph, has another long article[23] on the hemophiliacs of Bern. He lists several new family pedigrees which do not deviate from the recognized form of recessive sex-linked inheritance. He discusses the hematologic findings in so-called female carriers and claims to have demonstrated changes in the functions of the platelets and increased bleeding time in several

such individuals. He includes in his pedigree a child 3 years of age as a female hemophiliac, but unfortunately there were no clinical studies on this case.

The question of female hemophiliacs is creating increased interest. Rosenthal, Vogel, and Beres[24] present a detailed hematologic study of a female with the classical features of hemophilia. There were no other cases in the family of this patient, whose symptoms developed at the age of 28 years. The patient had a son who was entirely normal and the authors conclude that this case of hemophilia in a female was therefore genetically of different character from the hemophilia ordinarily seen in the male. The authors state that a careful search of the literature prior to the case reported has not yielded a single case of hemophilia in a female in which the hematologic criteria could be accepted.

Bauer and Meller[25] describe five cases in females who showed prolonged coagulation time and a familial incidence of the disease. Their data include a family in which the father and the mother were both hemophiliacs, and only one of their two daughters was a hemophiliac. They also report abnormalities in the bleeding time and platelet counts. The accuracy of this entire report is to be most seriously questioned. Studt[26] also believes that there is a quantitative abnormality in coagulation time demonstrable in female conductors. Birch[27] has prepared a monograph on hemophilia and includes a consideration of its genetic aspects.

Hereditary Pseudohemophilia.—This disease is to be sharply differentiated from hemophilia, both on clinical grounds and on those of genetic behavior. Clinically these cases present normal coagulation time. Handley and Nussbrecher[28] describe the occurrence of this disease in both male and female. Debré et al.,[29] in a study of seven families, confirmed the accepted hereditary pattern of dominant Mendelian heredity.

Other Hematologic Diseases.—Brockmann,[30] in a very careful study of seventeen families of individuals with polycythemia, found no increased frequency of the disease in these families and concludes that there is no relation to any constitutional disease entity. He believes, however, that a complex polyfactorial heredity is most probable. Wiskott[31] presents three cases of purpura hemorrhagica in three brothers. Four sisters were normal. Ardashnikov[32] describes a family pedigree of four generations with cases involving both sexes and transmitted directly from parent to child. The patients had increased bleeding time, normal platelets, and normal coagulation time. The hemorrhages were usually localized to the throat.

Macklin,[33] in a statistical analysis of cases of erythroblastosis foetalis reported in the literature, considers the relationship of this disease to icterus neonatorum and congenital anemia. She believes that the genetic behavior of these three diseases is sufficiently different to indicate a different genetic basis for each one. Pache[34] describes three families with severe jaundice of the newborn infant. He demonstrates that the percentage of diseased children is greater in later births.

Cardozo[35] attempts an immunologic study of sickling and blood groups and finds no definite relationship. Haden and Evans[36] studied a family of five white children, two of whom suffered from sickle-cell anemia, one with sickling but no anemia, and the other two with no blood dyscrasia. Bauer[37] studied a pair of 7-month-old identical twins, both of whom presented, on sternal puncture, a picture which the author con-

siders characteristic of von Jaksch-Hayem's anemia. Only one of the children had clinical symptoms of this disease.

Schemensky[38] describes a rare anomaly of the red blood cells characterized by an oval shape which is present under all circumstances. The condition was present in a mother and daughter. It has no clinical significance. Sternal puncture revealed a normal bone marrow. Strauss and Daland[39] describe a family with a similar condition in which ten individuals were involved. Heredity was typically dominant in character.

Gunn[40] reports the presence of hereditary acholuric jaundice in a strain of rats. This condition appeared by mutation in a laboratory strain of the animal. The author indicates the close similarity to the disease as it appears in human beings. Especially interesting is the fact that 50 per cent of normal-appearing hybrid rats showed increased fragility of the red blood cells and increased reticulocytosis, indicating that the condition is inherited as an incomplete dominant factor.

SKIN

The striking manifestations of hereditary skin conditions have given reports in this field a prominent place in the literature. An excellent summary of the available material up to 1933 has been prepared by Cockayne.[41] Munro[42] describes twenty persons with sebaceous cysts in four generations of a family and concludes that the disease is determined by a dominant gene subject to modification. West[43] describes a case of congenital ichthyosis in a mother and three sons. He concludes that the disease is determined by a dominant gene. He discusses Cockayne's analysis of heredity in this disease and dismisses that author's theory that it may be transmitted as a sex-linked recessive trait. West makes the error of assuming that the heredity of a disease must be explained by only one Mendelian mechanism. This is contrary to experience in both human and animal genetic material. Beres and Messeloff[44] describe a family in which ichthyosis vulgaris is inherited as a sex-linked recessive character. Idelberger and Haberler[45] describe a family in which the disease appears as a dominant character. Gilch,[46] in an exhaustive analysis of ichthyosis, describes several types of hereditary mechanism and attempts a clinical distinction on the basis of the different forms of heredity behavior.

Gillespie[47] describes four children in one family presenting total alopecia. The parents were related to each other but the author could not determine the exact relationship. A boy, 9 years old, presenting an ectodermal dysplasia is reported by Kerley.[48] Fitch[49] presents photographic evidence of the dominant inheritance of white forelock in four generations of one family. The abnormality was associated in some cases with white spots on the skin, while the latter occurred in one member without the hair anomaly. Anderson[50] describes an interesting family studied for four generations, presenting wooly hair in both male and female. The disease is transmitted only through affected individuals in direct line from parent to child.

McCrackin[51] describes a family of seven negro children, five of whom (three boys and two identical twin girls) suffer from albinism. In an elaborate summary article, Sanders[52] analyzes 140 families with 216 cases of albinism, gathered from the literature and his own experience. The heredity is typically recessive in character.

TEETH

Hyde,[53] in a general article directed to the dental profession, emphasizes the importance of heredity in various dental conditions, including double deciduous teeth, transparent dentine and enamel, congenital missing teeth, and hereditary hypoplasia.

Haldane[54] publishes a pedigree presented by C. H. Bampton to the Sixth International Dental Congress in 1914 in which the appearance of brown teeth was studied in five successive generations, and concludes that this anomaly follows a dominant sex-linked pattern, a type of heredity which is very rare.

The relationship of dental abnormalities to cleidocranial dysostosis is emphasized by Rushton.[55] The dental abnormalities he finds in the latter disease include supernumerary teeth, failure of eruption, deformities of the teeth, abnormalities of the jaw, and the formation of cysts.

EAR

Studies of the hereditary factors in diseases of the ear have been limited within the past year to congenital abnormalities of the external ear. Potter[56] presents a pedigree of a family followed for five generations in which a bilateral external ear malformation appeared to be transmitted as a dominant characteristic. Powell and Whitney,[57] who describe pedigrees of two families, conclude that free ear lobes are dominant, whereas adherent ones are recessive. They are criticized by Wiener[58] who believes that, although there is a correlation between types of ear lobes in parents and children, no definite genetic mechanism has been determined as yet.

EYE

A most unusual series of articles by Hamilton[59] undertakes the analysis of the entire population of Tasmania, with special reference to the incidence of hereditary eye diseases. He considers the problem from all angles, including social and economic significance of the various factors involved. The different hereditary eye conditions which have been found are described and analyzed from a genetic point of view. This study is of importance, not alone for the ophthalmologic material which it presents, but also as an example of a genetic study of the highest order.

Vogt and Meyer[60] present two families with angiomatosis retinae of the type associated with von Hipple-Lindau's disease. In one family father and daughter were affected; in the other, uncle and nephew. In the second case, there were two other uncles who had cerebellar tumors. The article is illustrated by beautifully colored plates demonstrating the lesions in the fundi. Walsh and Wegman[61] present a pedigree of hereditary cataract affecting the males more severely than the females. The data were submitted to Dr. C. W. Metz of the Carnegie Institute of Washington for an opinion of the genetic mechanisms involved. He made the suggestion: "Rather than speculate on the possible genetic basis of the cataract at present, it seems desirable to await the appearance of another generation which ought to provide significant information." Allan[62] presents a number of pedigrees of retinitis pigmentosa with several different forms of genetic behavior. This study suffers from the fact that of the fifty-nine patients, only fifteen were personally examined by the author. Two of the pedigrees were developed entirely

on the basis of hearsay information, and not a single individual in these families was examined. Bonnet and Paufique[63] described a father and three children presenting bilateral ophthalmoplegia. The father was the only affected member of eleven siblings.

White and Fulton[64] describe an unusual pupillary anomaly in monozygotic female twins. The anomaly consists of large, irregular pupils incapable of responding to constricting stimuli except in certain quadrants, which were the same in both subjects. The mother was reported to have the same condition. The father, five siblings, and five offspring were free of the abnormality.

Lisch[65] describes a family in which twelve members in three generations were afflicted with keratoconjunctivitis sicca. The author states that this is the first description of the familial incidence of this disease. Mann[66] describes three cases of congenital vascular veils in the vitreous, all in males, two in brothers. The author emphasizes the embryologic basis of this condition.

ORTHOPEDICS

The appearance of skeletal anomalies presents a complex problem which has been handled by two types of articles; broad surveys, in which an attempt is made to discuss congenital anomalies in general, and reports of the familial incidence of a given anomaly. Streeter,[67] in a Harvey lecture, discusses the general problem of congenital abnormalities, emphasizing their dependence on genetic factors. Macklin[68] offers a general statistical study of the relation of external factors, such as barometric pressure, to the etiology of malformation. She concludes that external factors are of little or no importance, heredity being the chief etiological factor. Müller,[69] in a monograph on the congenital abnormalities of the hand, discusses especially the developmental bases of the various abnormalities. He considers in detail the genetic factors involved.

Weidenmüller,[70] in a discussion of the heredity of spina bifida, emphasizes the importance of a careful search for mild atypical forms of the disease in supposedly normal members of the family. He describes a family with syndactylia in two generations and syndactylia and spina bifida in the third.

Schwarzweller[71] describes cases of congenital winged scapula and emphasizes the existence of associated anomalies such as fusion of vertebral arches, defects in the vertebral column, and scoliosis.

Pfeiffer[72] describes a variety of anomalies of the femur and concludes that in his cases the basic etiology is a genetic one. Schwarzweller,[73] in a discussion of acrocephalosyndactylia, emphasizes the presence in siblings of portions of this syndrome and its appearance with other hereditary anomalies. Hangarter and Dieker,[74] in a discussion of the Klipple-Feil syndrome, also emphasize the presence of minor abnormalities in other members of the family.

Jarcho and Levin[75] report a brother and sister with a form of the Klipple-Feil syndrome. They postulate the existence of a general dysplastic tendency, which is evidenced in these cases and in other members of the family by the existence of minor abnormalities, such as accessory nipple, anomalies of the heart, and undescended testicle. A second specific dysplastic factor is considered to be responsible for the deformity itself. An interesting observation which the authors made was that corresponding to the reduced number of vertebrae in the

thoracic region there was also a reduction in the number of thoracic spinal roots. They conclude, therefore, that the so-called "segmentation of the spinal roots really depends upon extrinsic structures rather than upon a fundamental pattern within the nervous system."

Bakwin and Krida[76] present a brother and sister with x-ray evidence of metaphyseal dysplasia. Fused fingers were present as a dominant hereditary characteristic in a family studied by Wightman,[77] with data for seven generations. Jackson[78] describes a family in which six digits appeared as an irregular dominant factor for four generations. Duncan,[79] in an article written from a therapeutic point of view, presents a pair of identical twins with coxa vara, the deformity in one being the mirror image of that in the other.

Achondroplastic nanism, associated with musical ability, appeared as a dominant nonsex-linked characteristic in a family known personally to Capinpin.[80] Volhard and Drigalski[81] describe a family in which three brothers present a peculiar deformity of the spine. They mention a family with a similar picture described by Nilsonne in which also only males were affected. Gaugele[82] discusses congenital dislocation of the hip. Though he recognizes its increased familial incidence, he doubts that it is a hereditary disease.

GENITOURINARY DISEASE AND SURGERY

Gruber[83] presents a detailed analysis of a variety of congenital anomalies of the genitourinary system. He discusses especially pedigrees of families with cystic kidney. He describes the relationship of this anomaly with other anomalies, especially those involving the skeletal system. There is an extensive bibliography. Gordon and Trasoff[84] describe a family in which five children out of seven have polycystic kidney. The parents of these children were related as uncle and niece. The author stresses the importance of examining all members of a family in which polycystic kidney occurs.

West[85] presents two pedigrees illustrating the familial incidence of hernia. His data do not allow a definite conclusion as to the Mendelian mechanism involved.

A case of unusual interest is described by Pettersson and Bonnier.[86] The patient was a girl, apparently normal, who was operated upon for double inguinal hernia and was found to have testes and other internal male structures but no internal female structures. Examination of the family revealed similar sex mosaic inheritance among other individuals. The authors discuss possible genetic explanations of this inherited anomaly but do not arrive at a final conclusion. They consider it most probable that the individuals begin as normal males but that a sex-linked recessive gene inhibits the development of the external male genitals.

CANCER

In the articles so far discussed several cases have arisen in which a hereditary factor has been pointed out as of significance in the development of an individual type of tumor growth. Examples of this are von Hipple-Lindau's disease and sebaceous cysts.

One must, however, make a sharp distinction between heredity as regards a specific type of unusual growth and the heredity of cancer in general. With regard to the former, a great deal of information is available. With regard to the latter, there is little convincing material

to be found in human studies. Little and Reimann,[87] in an unusual paper, present a discussion on the subject of heredity in relation to neoplastic disease, which is valuable as an indication of the problems which are being emphasized in studies of this subject.

Bell and Rothnem[88] describe two cases in brothers aged 16 and 13 years who had xeroderma pigmentosum with carcinoma. The parents were second cousins. Hauser and Weller[89] describe additional cases in the so-called cancer family of Warthin, in which forty-one individuals out of a total of 174 over 25 years of age have some form of neoplasm. Twenty-six of these were carcinoma of the intestinal tract, and fifteen were of the uterus. No definite Mendelian mechanism was indicated. Martynova[90] studied the families of 201 women who had carcinoma of the breast. Seven hundred and ninety-six patients from a dental clinic were used as controls. In the families of the cancer patients there was an incidence of carcinoma, in general, of 12.08 per cent and of cancer of the breast of 2.65 per cent. Among the controls the general incidence of cancer was 2.96 per cent and cancer of the breast 0.17 per cent. This study would seem to indicate the operation of a very definite hereditary factor. Körbler,[91] in his presentation of several cases of familial incidence of cancer, poses the problem of the basis of this increased incidence. He considers heredity and contagiousness to be possible factors but he leaves the problem unanswered because of insufficient available data.

In the consideration of cancer heredity, animal experiments are of interest. Stark[92] describes an interesting study in the Drosophila melanogaster, which has been the animal most used in genetic studies. He describes several different hereditary tumors presenting a variety of hereditary mechanisms. One was sex-linked, never being seen in the male because all males who were afflicted died before reaching maturity. Another type due to multiple genes in several chromosomes is described. Some of the tumors arise from embryonic rests in the walls of the larval digestive tract. Another form resembles lymphosarcoma, another melanoepithelioma. The importance of this study is that it allows detailed genetic investigation of definite neoplasms presenting certain histologic similarities to human material. Murray[93] describes the relation of genetics to transplantation of neoplastic tissue and emphasizes the importance of genetic factors in the success of transplantation experiments in animals.

Bittner,[94] in a review of the genetics of cancer in mice, warns against the application of findings in animal experimentation work to the human problem. He says: "The impossibility of securing human data to compare with inbred strains of animals where controlled matings may be made needs little comment. The reliability of considerable of the human data is questionable and leaves much to be desired."

ENDOCRINE DISEASES

Two papers of extreme interest have been published in which endocrine disturbances in one of a set of identical twins have resulted in gross dissimilarity in the individuals. In all the cases the identity of the twins was established by the usual biologic criteria. Lüth[95] describes three sets of identical twins with differences in growth and development in one individual of each set. Lewis[96] describes in detail two brothers who until puberty were always mistaken for each other. After that, one grew larger than the other and developed acromegalic features.

He grew to a height of 6 feet, 4 inches, while his brother was 5 feet, 8 inches. The only etiological clue in the former was a head injury sustained at the age of 12 years.

Munro[97] describes two cases in brother and sister with a similar atypical and uncommon psychosis associated with endocrine malfunction suggestive of the hyperactivity of the adrenals or of the anterior pituitary. The parents were first cousins.

Warkany and Mitchell,[98] in a discussion of heredodegenerative diseases, warn against the tendency to assume a relationship to endocrine disease, even when both may be present in the same patient. Goldman and Smith[99] describe several cases of hyperparathyroidism occurring in siblings.

Laurence-Moon-Biedl Syndrome.—A great deal of interest has been manifested in this disease. The syndrome contains in its complete form the following manifestations: mental defect, retinitis pigmentosa, adiposogenital dystrophy, syndactylia, polydactylia, microglossia, and various skull defects. The disease has a definite familial incidence, though any one individual may have varying degrees of the affliction, from the disease in its entirety to the appearance of isolated features. Warkany and Frauenberger,[100] in a detailed study of the literature, emphasized the fact that the syndrome rarely appears in its full form. They conclude that the syndrome does not represent a disease entity but is rather a combination of more or less frequent heredofamilial symptoms.

Van Bogaert[101] describes a family in which two brothers have the disease in its classic form, while the mother had only retinitis pigmentosa and two aunts had obesity, hypogenitalism, and mental disturbances. Panse[102] also discusses the hereditary basis of this disease. Cooperstock[103] accepts the explanation of two recessive linked genes to account for a large family he studied, the various members of which had one or more stigmas of the syndrome.

NEUROLOGY AND PSYCHIATRY

The problem of hereditary factors in nervous and mental diseases has aroused the interest of physicians, sociologists, and geneticists for practical as well as theoretical reasons. Much data have been accumulated, particularly by German authors, and many conclusions, both correct and erroneous, have been drawn. An excellent critical analysis of the entire subject has been prepared by a special committee appointed by the American Neurological Association to investigate the problem of eugenic sterilization. This committee, consisting of Drs. Abraham Myerson, James B. Ayer, Tracy J. Putnam, Clyde E. Keeler, and Leo Alexander, have presented the results of their studies in a book entitled ***Eugenical Sterilization,***[104] to which repeated references will be made in this review. Additional sources of critical evaluation of the data relating to heredity of mental and neurological disorders is to be found in the publications of the English scientists, who have given to this subject a series of brilliant and basic works, those of Hogben,[105] Haldane,[3] and Penrose[106] being especially valuable.

Huntington's Chorea.—Huntington's chorea, which is a classical example of dominant heredity in the human being, has been reported by a number of different authors. Spillane and Phillips[107] describe twenty-four cases with typical dominant heredity, and explain those instances

in which both parents of afflicted individuals were normal by the assumption that the affected parent died before he was old enough to manifest the disease. Hempel[108] describes several cases with typical heredity but with atypical clinical pictures that created considerable difficulty in diagnosis. Meierhofer[109] in his paper stresses the appearance of atypical psychoses in a family afflicted with Huntington's chorea. Stone and Falstein[110] describe a group of cases with atypical heredity.

Minski and Guttmann[111] offer a detailed analysis of thirty-four families, considering also the clinical manifestations of the disease in its usual and unusual forms. Their data confirm the accepted mechanism of dominant heredity.

Familial Ataxia, Multiple Sclerosis, and Related Diseases.—Hall and MacKay,[112] in an excellent paper, describe two forms of familial ataxia and emphasize the diagnostic difficulties involved in differentiating this disease from multiple sclerosis. This point is very important in the evaluation of several articles which have appeared in the German literature in which multiple sclerosis is described as a hereditary disease. Curschmann[113] describes three brothers afflicted with a disease diagnosed as multiple sclerosis. Jentsch[114] describes two sets of identical twins with a disease diagnosed as multiple sclerosis. He considers it to be an infectious disease with a hereditary predisposition. Curtius and Speer,[115] in a general analysis of the subject, consider multiple sclerosis to be forty times as frequent among the relatives of patients affected as in the general population.

Schröder[116] describes a family in which two brothers, one sister, the mother, and the maternal grandmother had Friedreich's ataxia. Lux[117] considers hereditary ataxia as an hereditary disease in which the clinical course is profoundly affected by external factors, such as intercurrent infections. In a paper on hereditary cerebellar ataxia by Waggoner, Löwenberg and Speicher,[118] the difficulties of diagnosis and classification are strongly brought out. The report includes the pathologic study of a patient and genetic study of five generations of the patient's family, which included twenty-seven cases of ataxia. The pathologic study showed abnormalities in the pons, olivary bodies, and the cerebellum. The authors, however, refuse to consider this a case of olivo-pontocerebellar atrophy, and on the basis of the heredity, classify this as an example of the heredocerebellar ataxia of Pierre Marie.

Two papers on familial spinal spastic paralysis describing a familial incidence interpreted as due to a dominant hereditary factor are presented by Röhricht[119] and Kahlstorf.[120] The fact that the authors describe the same disease under different names is an indication of the difficulties that beset analysis in this field. Turner and Roberts[121] describe a sex-linked heredity in a condition resembling Friedreich's ataxia. This has never before been reported in this disease.

The myelopathies, of which there are so many types, present striking examples of heredity in organic neurological disorders. Two general reviews on the subject are available, one by Aring and Cobb[122] in English, and one by Sjövall[123] in German. The diagnostic difficulties in differentiating the various types of this disease must be taken into consideration in evaluating the reports which follow. Boeters[124] describes a large series of cases involving the various forms of myelopathies. Cooper[125] presents a history of a 55-year-old man and three sons, ages 28, 24, and 21 years, who had Dejerine-Sottos disease. In addition, one

other member of the family had muscular atrophy, and a maternal grandmother presented wasting of peripheral portions of all limbs. Rütenik[126] describes a case of amyotrophic lateral sclerosis (confirmed at autopsy) with a family history including a sister who had had the same symptoms and a brother with early symptoms which were discovered by routine examination of the family. Schneider and Abeles[127] present clinical histories of two brothers with a Charcot-Marie-Tooth syndrome associated with primary optic atrophy. The parents were first cousins. A case of myotonia congenita in a boy 9 years of age is described by Breitfort.[128] There was no other case in the family.

Rothbart[129] describes the occurrence of myasthenia gravis in four brothers. This disease is not usually considered to be a hereditary one, the only evidence heretofore having been the occasional coexistence of myasthenia and congenital anomalies. This report therefore assumes increased importance.

Heredodegenerative Diseases.—An interesting report of Niemann-Pick's disease in a set of identical twins is described by Freudenberg.[130] He emphasizes the "Aryan" descent of these patients. There were no reports this year of heredity in amaurotic family idiocy of the infantile type which is pathologically and clinically closely related to Niemann-Pick's disease. In the former there is strong evidence that heredity is determined by a single recessive gene. Van Bogaert and Borremans[131] present a series of cases which they consider to be an adult form of amaurotic family idiocy. The clinical details make very questionable the accuracy of their diagnosis and further observation is necessary. Jakobsen[132] describes a case of juvenile amaurotic family idiocy in which the patient was the only afflicted member of a family in which four generations were studied.

Two papers on Wilson's disease have appeared. Schwyn[133] describes two cases occurring in brother and sister, and includes a detailed pathologic report. Müller[134] describes a case in a boy with a suggestive family history. The father had pernicious anemia and combined sclerosis, and a sister died of a disease manifesting extrapyramidal symptoms. He considers the disease to be determined by a metabolic anomaly that may affect different organs.

Forsberg and Stromme[135] describe a family in which a brother and three sisters had dysarthria, spastic phenomena, cerebellar ataxia, and nystagmus. The grandparents were cousins. The authors have diagnosed these cases as Pelizaeus-Merzbacher disease but offer no anatomic confirmation.

The pathogenesis of congenital diplegia has caused considerable discussion. Alpers[136] in a recent review of the subject agrees with the prevailing general opinion that it is a degenerative disease, probably due to the effect of prenatal factors. The theory of birth injury as a causative factor has steadily lost in acceptance in the years that the subject has been studied. In an important paper by Thums[137] there is an analysis of a series of twins in which one or both members were afflicted with Little's disease. His findings are very striking. Among nine pairs of identical twins only one pair presented the appearance of the disease in both individuals. Among ten sets of nonidentical twins there is no case in which both had the disease. In a group of ten sets of twins of different sex and therefore biovular, one set presented the disease in both individuals. Lisch and Thums[138] analyze a pair of identical

twins, one of whom was entirely normal, whereas the other suffered with congenital spastic diplegia and mental deficiency. The diagnosis of identity was made on the basis of the accepted biologic criteria. This paper apparently proves that the disease is not determined on a purely hereditary basis.

Van Bogaert and de Savitsch[139] describe a group of cases which they cannot classify exactly, in which rhythmic tremor of the head, eyes, and upper extremities presents the outstanding clinical features. Forty members of a family of 109 individuals were afflicted. The data were interpreted as presenting evidence of a dominant type of heredity.

Russell and Tallerman[140] describe the occurrence (confirmed by autopsy) of familial progressive diffuse cerebral sclerosis in two Jewish children whose parents were first cousins and whose two siblings were normal.

Other Conditions.—Allan[141] studied seventy-two consecutive cases of parkinsonism. In forty-five he found a positive family history, of which he presents forty-three complete pedigrees. He considers the genetic mechanism to be that of an autosomal gene acting as dominant. The author indicates the incompleteness of his study, emphasizing the need for observation by other workers, and claims only that he has demonstrated beyond doubt the importance of heredity in shaking palsy.

Menninger and Grotjahn[142] studied a group of cases of juvenile dementia paralytica and conclude that the tendency for neurosyphilis to appear with increased frequency in a family is due to the existence of a neurotropic strain of *Spirochaeta pallida* rather than to familial predisposition to cerebrospinal syphilis.

Laubenthal[143] describes a family presenting several individuals with congenital word blindness.

Craig[144] describes the interesting occurrence of intracranial tumors in two sisters. The symptoms developed in both patients at approximately the same age. One of the patients had a craniopharyngioma and died postoperatively; the other had a primary glioma of the optic chiasm and recovered following surgical intervention. The case of a boy 19 years of age with intraocular neuroma of the optic nerve head is described by Stollard.[145] The patient subsequently developed signs of increased intracranial pressure. There were in the family of the patient several cases of multiple neurofibromas of the central nervous system and cranial nerves, in two generations.

In a study of sciatica, involving seven sets of identical twins and eight sets of fraternal twins, Becker[146] postulates the existence of a hereditary predisposition to this disease which is, however, brought out by various environmental factors.

The Epilepsies.—It must be recognized that in using this term one includes a heterogeneous group of diseases which are better described under the general heading of convulsive disorders. The reports which have appeared on the hereditary basis of this disease have almost universally indicated an increased incidence in the families of afflicted individuals, the conclusion being that in epilepsy one is dealing with a disease which is basically hereditary in character. Conrad[147] has published an elaborate series of articles consisting of a study of twins and of the familial incidence of the disease as compared with that in the general population. His general conclusion has been that the disease is basically a hereditary one, and he has pointed out that the incidence is

twenty to thirty times as great in families of epileptics as in the general population. Paskind and Brown[148] attempted to differentiate the so-called institutional deteriorated type of epileptic from the nondeteriorated, well-adjusted, ambulatory patient. They find a smaller incidence of so-called neuropathic taints in the families of nondeteriorated patients than in the families of deteriorated patients. This search for neuropathic taints, which characterizes the paper of Paskind and Brown, is to be found in most studies of the heredity of mental disorders. It raises the general question of so-called polymorphism, under which term one makes the assumption that a poor hereditary constitution may manifest itself in one of several abnormal traits. This conception is subjected to severe criticism by the Committee of the American Neurological Association. In this work the opinion is stated that so far no conclusive studies have appeared which justify this lumping together of a variety of abnormalities under the one general group. It must be remembered that no advance in knowledge is achieved by giving to an unknown entity a new and longer name.

Franke[149] studied the children of epileptics, distinguishing between so-called true epilepsy and symptomatic epilepsy. He found a lower incidence of epilepsy and other mental defects among the children of the symptomatic group. The Committee of the American Neurological Association devotes considerable space to the subject of heredity in epilepsy and concludes that epilepsy occurs more frequently in the descendants of the epileptic than in the descendants of the nonepileptic, and also agrees that the vast bulk of epileptics arise from families having a low incidence of epilepsy and who, in the main, are indistinguishable from the mass of the population. They hold forward little hope at present for the effective eradication of epilepsy on the basis of its eugenic control.

Latham and Munro[150] describe a family in which the parents were first cousins and in which five out of eight siblings present myoclonic epilepsy and deaf-mutism. Other members of the family showed what the authors call psychosis of the affective type. This is the first recorded example of the coexistence of these anomalies. Minkowska[151] also emphasizes the coexistence of epilepsy and psychosis in a very long report attempting to establish a basic relationship between these two conditions. Keschner[152] presents the clinical history of an unusual case of myoclonic epilepsy in a 46-year-old man whose maternal aunt had a similar disease; one second cousin was epileptic, and one third cousin had a myoclonic convulsive condition. The patient's brother suffered from multiple sclerosis and ataxia and was feeble-minded, but never had convulsive seizures.

Mental Deficiency.—Under the general heading of mental deficiency, Mongolian idiocy is the one clear-cut entity. Doxiades and Portius[153] present an elaborate study of mongolism, from which they conclude that the condition is twenty times as frequent in families presenting the disease as in the general population. They find also the presence in mentally normal relatives of single anatomic characteristics usually associated with the disease. They recognize the well-established fact that the disease is more common among the children of older mothers. Schröder[154] considers that the hereditary basis of this disease is highly suggestive but not proved. Bleyer[155] presents an interesting analysis of the relation of maternal age to the incidence of mongolism, based on

2,822 cases, and presents very strong evidence that the age of the mother is an important factor, the disease being far more common among the offspring of older mothers. It appears that mongolism is a disease in which two important factors operate: heredity and prenatal environment. On this basis, the various apparently conflicting theories can be reconciled. This interpretation is developed in detail by Penrose.[106]

Lahdensuu[156] in a study of Mongolian idiocy in Finland, collected 250 cases. He considers heredity to be the basic factor and does not believe the age of the mother to be of importance. In this regard his experience is contrary to that of most other observers. An unusual case report of paraplegia and mongolism occurring in twins is offered by Gordon and Roberts.[157] The twins, both girls, were considered to be fraternal in type. One had only moderate manifestations of both the paraplegia and mongolism. The intelligence quotient of one twin was 59; the other 89.

An interesting animal experiment presenting a similar genetic relationship to that found in mongolism is described by Haldane,[3] in discussing a paper by Wright on heredity of polydactylia in the guinea pig. In a given strain, in which polydactylia is present, it was found that the percentage of newborn infants presenting this condition varied according to the age of the mother, younger mothers having over 80 per cent polydactylic offspring, while older mothers had 30 per cent polydactylic offspring. This illustrates the coexistent effect of hereditary and environmental factors in the development of a characteristic, the essential basis of which is hereditary, and the environmental factor prenatal.

In considering other types of mental deficiency, one is faced with enormous difficulties which are basically due to the lumping together of all forms of mental deficiency with scarcely any knowledge of the underlying pathology or basic etiology of the condition. Hogben[105] in a discussion of human inheritance has most eloquently indicated the danger of applying elaborate mathematical analysis to data which are basically inadequate when he says: "There is the danger of concealing assumptions which have no factual basis behind an impressive façade of flawless algebra."

Rosanoff, Handy, and Plesset,[158] in an elaborate monograph, analyze 336 pairs of twins with mental deficiency in one or both of the pair. They conclude that the hereditary factors play an important part but are not the only ones involved. They conclude from their data that sex-linked genetic factors also operate in the manifestation of this condition on the basis of the greater incidence of mental deficiency among males.

A special committee appointed by the British Research Council has prepared a study of 1,280 cases of mental defects in which the existence of hereditary factors is emphasized.[159]

The Mental Deficiency Committee of the Royal Medico-Psychological Association[160] in an analysis of the relatives of normal individuals found an incidence of mental defect and psychologic abnormality, including psychosis, in 57 per cent of the families of these normal persons. This figure is compared with the usually quoted one, that 80 per cent of mental defectives have positive family histories. This article is of basic

importance as an indication of the difficulty of determining hereditary significance in a disease by the method of studying the general familial incidence.

Jervis[161] presents a preliminary study of fifty cases of mental deficiency associated with urinary excretion of phenyl pyruvic acid and concludes that both the involvement of the nervous system and the metabolic error in these patients are an expression of the same degenerative processes, genetic in character.

Schwesinger,[162] in an exhaustive analysis, indicates that the degree of intelligence of a given individual is in large part determined by hereditary factors. However, the mechanism of this heredity is most complex and no detailed knowledge is available at present. Environmental factors too are of vast importance in the development of the inherent intellectual capacities of the individual. This would indicate the caution with which one should approach this problem. It is doubtful whether, in the present state of knowledge, any effect on the incidence of mental deficiency would be achieved by eugenic measures.

One may also bring up at this time the question which has frequently been raised as to whether or not feeble-minded and other mentally defective individuals are propagating at a rate which threatens the survival of our civilization. The Committee of the American Neurological Association, in analyzing this point, brings out quite clearly that statistical data show that there is no indication of increased fertility among feeble-minded or other mental defectives and that actually their rate of reproduction is lower than that of the general population.

A book by Dubitscher[163] on mental deficiency has just appeared. It assumes unusual importance because it is an official publication appearing under the direction of Dr. A. Gütt, who carries the title "Ministerialdirektor im Reichs- u. Preuss. Ministerium des Innern. Prasident des Preuss. Landesgesundheitzrates." The book is the first in a series which will cover other diseases in which heredity is considered to be important. The expressed purpose of the work is to justify the sterilization laws which have been put into effect by the German government. This volume includes a detailed summary of the clinical and pathologic aspects of feeble-mindedness and on this account is of great value. It presents no new data with regard to the genetic aspect of the problem.

Psychosis and Neurosis.—It is a truism that among the many schools of psychiatry there is the greatest divergence of opinion regarding all matters concerning mental diseases. This lack of agreement is manifest in considering etiology, pathogenesis, clinical manifestations, psychodynamics and prognosis.

It was pointed out in the beginning of this review that one of the basic elements for a valid study in heredity is the diagnostic accuracy of the clinical material. Certainly in a subject as complicated as that of the mental diseases, the clarity of clinical thought which would allow an author unquestioned confidence in his material is not possible. Unfortunately, most papers on heredity in psychoses and neuroses are concerned more with statistical acrobatics and conclusions concerning the fate of the human race than with a clinical evaluation of the material presented.

An example of an elaborate study in which the author goes so far with his genetic formulas as to diagram the position of the genes for schizophrenia in the chromosomes is found in a paper by Ziehen.[164] Schnitzen-

berger,[165] in a study of the incidence of mental disease among the relatives of thirty patients with involution melancholia, found among the parents of the patients 5.31 per cent of affective psychoses. In 138 siblings there was no other case of involution melancholia, but there were 3.3 per cent of affective psychoses. These figures indicate no greater incidence than in the general population. In this regard one may recall the findings of the Mental Deficiency Committee of the Royal Medico-Psychological Association in which the incidence of psychoses and neuroses among the relatives of normal persons was studied and found to be 23 per cent.

McInnes[166] studies the comparative incidence of neuroses in the families of fifty patients with anxiety neurosis and thirty with hysteria. He had seventy-five control families. Among the controls the parents were normal in 72 per cent of the cases and siblings in 70.6 per cent of the cases. In the families of his patients only 46 per cent of the parents and of the siblings were normal. Among the patients with hysteria, on the contrary, the percentage of normal parents was higher than in the controls; that is, 93.4 per cent. Among the siblings 16.6 per cent of the cases presented symptoms of hysteria. The study was conducted by the questionnaire method. There is no discussion of possible environmental factors in these cases. An important paper bearing on this point is one by Powdermaker,[167] presented by the author at the Third International Congress of Eugenics in 1932, in which an attempt is made to weigh the relative importance of nature and nurture in mental disease. The author emphasizes the unusual abnormal environment that is created for a child when one or both parents are suffering from a mental illness.

The Committee of the American Neurological Association gives considerable space to the problem of heredity of mental disease. They emphasize the point that the various conditions being discussed, such as schizophrenia, manic-depressive psychosis, feeble-mindedness, and epilepsy are probably each of heterogeneous composition and that all considerations of this problem must keep in mind this limitation. They consider unfounded the tendency to lump together various mental illnesses as indicative of a so-called neuropathic trend, a subject discussed above when considering polymorphism. They state that most of the early conclusions which are extensively quoted to prove the heredity in these various diseases were "merely statistical illusions due to the artificial elements of selection." They emphasize also the lack of adequate control studies in most cases. They conclude, however, that "in spite of criticism we have made of the above material, it is probable that there is some hereditary factor operating in dementia praecox, although it cannot be stated that this has been satisfactorily demonstrated in a clear-cut, inconvertible way." Their discussion of manic-depressive psychosis too is most surprising. They say: "It is curious to note that while the literature is quite unanimous as to the hereditary character of manic-depressive psychosis, very little valuble statistical material is available." They believe that the studies presented indicate an increased incidence of the disease among siblings of patients as compared with the general population. They conclude as follows: ". . . fewer cases than in schizophrenia have been studied, and the statistical value of most of the publications is not high. It is safe to say that manic-depressive psychosis is inheritable."

It is our opinion that this conclusion is not warranted either by the original data under review or by the arguments presented by the Committee. We believe the facts indicate an increased familial incidence of mental illness, still to be adequately measured and due to unknown factors. Future study should demonstrate the relative importance of heredity and environment in these diseases. At present there is no reason to venture any conclusion beyond the facts, especially because of the tendency in some places to apply drastic sterilization laws, not alone to patients with mental illness but also to their relatives.

Kretschmer,[168] in a general article, summarizes his well-known theory of the relation of heredity and constitution to mental disease. He assumes that there is a hereditary basis for schizophrenia and manic-depressive psychosis. He describes certain physical types which present a definite tendency to develop in each case a specific variety of mental illness. The basic types he considers "radical forms of personality." He emphasizes, however, that the psychosis is subject to environmental factors. He says: "Often external experience is not so much the real cause of a neurosis; it is rather a flame which ignites the inner typologically determined mass of conflicts within the personality."

HEREDITY AND EUGENICS

There are a number of reports which are directed mainly toward the general problem of heredity, using human material only as the means of establishing some basic genetic point. These papers are, however, of no less interest to the clinician and usually are of greater value as careful genetic studies than the more definitely clinical papers.

The study of twins has afforded an approach to the study of human genetics, the full benefit of which is still to be realized. Newman, Freeman, and Holzinger[169] have published in a book the results of many years of study. The book presents the product of collaboration of a biologist, a psychologist, and a statistician. It is a careful critical analysis which warrants careful reading by any student of the subject. Their conclusions are drawn with great caution. It is not practical to present a summary of this book at this point.

Schiller[170] describes an extensive study of 214 pairs of twins, of which eighty were identical twins. She studied a variety of characteristics and confirms the accepted findings with regard to similarity of body size, pigmentation, and other bodily characteristics in identical twins. She adds considerable data regarding similarities in capillary patterns in identical twns. The greatest difference in identical twins was in their characters and emotional expressions. Lehmann[171] also emphasized the importance of capillary studies as a means of establishing identity in twin sets. A monograph by Brander[172] discusses the study of twins with special emphasis on its relation to pediatrics.

Studies regarding Mendelian mechanisms in human material are obviously difficult to carry out, but the recent literature has been unusually rich in this regard. Several papers have been published on linkage, evidence of mutation, and other genetic manifestations previously studied only in animal material. Haldane,[173] in a study of hemophilia, points out that hemophiliacs die young and have a low fertility rate, despite which the percentage of hemophilia in the population has remained constant. The assumption is that the loss of genes by the early

death of hemophiliacs is replaced by mutation. In this way are explained the not infrequent cases of hemophilia in which no family history is obtained.

Riddell[174] describes a family in which hemophilia and color blindness, both of which are sex-linked characters, are present in the expected linked relationship. Bell and Haldane[175] discuss in detail the mathematical implications of this relationship. Csik and Mather[176] describe a group of cases including oligophrenia, Laurence-Moon-Biedl syndrome, harelip, cleft palate, and allergy, in all of which there has been described an excess of affected males. This has usually been ascribed to sex linkage of some of the genes concerned in their inheritance. The authors consider the data insufficient to explain adequately what is the mechanism behind the difference in incidence of these diseases in the sexes.

The hereditary blood groups have afforded an opportunity for genetic study in human beings unequaled by any other character, due to the universal appearance of blood groups in all individuals. Friedenreich[177] presents a general summary of the subject. Hogben and Pollack,[178] in a study of several cases of Friedreich's ataxia, emphasize the value of carrying out with all genetic studies a detailed investigation of the blood groups and taste deficiency. The aim of such studies is the accumulation of data regarding linkage relationships in human material. In recent years it has been established that taste deficiency to a variety of substances is an inherited characteristic. All individuals present either the ability to taste these substances or the inability to taste them. The evidence indicates that deficiency of taste is a recessive factor. Studies of taste deficiency are indicated in all genetic human studies.

Snyder and Davidson[179] describe the inheritance of taste deficiency to diphenylguanidine as a recessive factor. Gottschick[180] obtains a similar result in a study of p-athoxyphenylthio acid. Boyd and Boyd[181] carried out an extensive study of taste deficiency and pointed out certain complexities in the problem due to differences in distribution of tasters and nontasters in different anthropologic groups. Studies were carried out in Dublin, Wales, Russia, and Egypt. They emphasized that there are fewer tasters in the males than in females. The significance of this finding is not yet clearly understood.

Herman and Derby[182] studied the relation of the blood group properties A, B, M, and N to mental disease. They found no significant distribution of the blood group properties to exist in mental disease.

Faust[183] presents a theoretical, statistical analysis of the probability that a given individual is the carrier of a defective gene. This is based on incidence of the disease in the relatives, its frequency in the general population, and the mechanism of its heredity. The weakest link in this elaborate statistical structure is that the method is applied to such diseases as schizophrenia, in which not only is there no adequate proof of a mechanism of heredity but even the degree of significance of hereditary factors is not entirely established.

One should mention at this point a new journal[184] which has made its first appearance this year, devoted to review articles on heredity, race hygiene, and related subjects. Verschuer[185] has put out a book on human heredity in which he describes the indications for sterilization, listing as the diseases in which this procedure is most frequently carried out the following conditions: congenital feeble-mindedness, schizo-

phrenia, manic-depressive psychosis, hereditary epilepsy, Huntington's chorea, hereditary blindness, hereditary deafness, serious hereditary bodily malformation, and serious alcoholism.

Summary.—There exists in the literature on human heredity a tendency for the selection of cases presenting a positive hereditary history. This would result in overemphasis on the whole of the importance of heredity as a factor in the pathogenesis of disease. There is also the mistaken impression that when a disease is proved to be hereditary nothing can be done for the patient. It is perhaps for this reason that in most discussions of the subject by clinicians there enters a feeling of futility regarding the therapeutic approach to the cases under consideration.

Actually, one must realize that in the development of any clinical syndrome there are always the two factors, variously termed intrinsic and extrinsic, hereditary and environmental, or nature and nurture. The significance of this is that no discussion of the cause of a disease is complete which assumes only a hereditary basis or only an environmental basis. The task is to weigh the proportionate importance of each. Stated practically, this means the need of determining what environmental factors the physician can bring into operation to overcome the hereditary factors which are obviously beyond his control. For example, in such a disease as hemophilia it is apparent that the hereditary factors are the predominating ones. The physician may, by repeated blood transfusions (an environmental factor), modify the course of the disease. His therapy is at best most unsatisfactory. The correct procedure in the broad sense is to avoid the birth of hemophiliac individuals, which calls for eugenic measures. In cases such as this there is no disagreement.

An example of a disease in which heredity is an unquestionable fact, yet one in which the environment is of striking importance, is the group of allergic diseases. Here heredity determines that an individual can become allergic and so develop asthma, hay fever, and other allergic manifestations. However, in order for the disease to appear certain environmental factors are necessary as, in the case of an individual susceptible to ragweed, the presence of ragweed pollen in the atmosphere. Furthermore, it is possible for the physician to modify the clinical course of this hereditary disease by a variety of therapeutic measures. Certainly in this disease the therapeutists have not taken a fatalistic attitude.

At the other extreme are a group of diseases in which heredity may play a part but in which at the present time no conclusive evidence for this has been presented. The mental diseases present the most striking examples of this group. Here the proved genetic data are so scarce that no practicable eugenic plan can be presented for the elimination of these diseases. The optimistic claims of eugenicists, as exemplified especially in the noncritical enthsiasm of certain authors abroad, is not justified by careful and sober study. It would seem that with the present state of knowledge the wiser approach both therapeutically and as a preventive measure would be the environmental aspect, namely a psychotherapeutic and socio-economic one.

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Panel Discussion on the Role of Allergy in Pediatric Practice

Chairman: Dr. Bret Ratner, New York.

Assistants: Dr. Francis Scott Smyth, San Francisco.
Dr. Albert H. Rowe, Oakland.
Dr. George Piness, Los Angeles.

PRESIDENT PHILIP VAN INGEN.—This panel discussion will be conducted by Dr. Bret Ratner; there will be no questions asked from the floor. Anybody who wishes a question will please write it, send it to the table. It will be answered during the evening as far as possible.

CHAIRMAN RATNER.—It is indeed a privilege to be invited to be chairman of this panel. My teacher, Dr. Schloss, told me that he had to decide soon after he started work in the allergy field, whether he was to become an allergist or remain a pediatrician. I have unwittingly been placed in the same dilemma and find to my disappointment and chagrin that the allergists insist that I am a pediatrician and the pediatricians make it known that I am an allergist.

My own feeling is that the time has arrived when allergy must become an integral part of pediatrics. You will hear Dr. Smyth, the other pediatrician on this panel, express the same idea.

The situation is not unique; the pediatrician finds that he must include within his province such fields as psychology and endocrinology. The purpose of this panel therefore is to show how important a role allergy plays in the practice of pediatrics.

Our knowledge of the basis of allergic diseases is incomplete. Problems we are unable to solve beset us. After most painstaking studies and treatment our patients may continue to scratch or wheeze unmercifully. At times when we are delighted with the remission of all symptoms for many months and when we feel that we have obtained a brilliant result, the child has a sudden return of symptoms, and we are confronted by a disappointed mother who in consternation declares that after all we have not cured her child. Nevertheless, it is gratifying to know that in a large number of cases the well-trained allergist obtains good results.

The men working with allergy in the adult have found that a large proportion of their patients date the onset of their symptoms from childhood. Those who have made observations on allergic children find that the onset of allergy often occurs very early in life. My own observations indicate that 50 per cent of our cases have had their onset of symptoms in the first year and that by the eighth year 80 per cent of our children have manifested their allergic symptoms; by the tenth year practically all of our patients have developed symptoms. It is apparent from this that the pediatrician must be ever watchful for early allergic symptoms.

There are many problems which we would like to clarify for you, but in the short time allotted we cannot hope to do more than present some of the phases which may confront you, and make suggestions which we believe may be helpful.

I am particularly fortunate in having associated with me men whose contributions in the field of allergy have been noteworthy and whose opinions are mellowed by broad experience.

The first problem with which we will concern ourselves will be the early manifestations of allergy in infants. Since I know of no one better qualified to speak on this topic than Dr. Smyth, I shall ask him to open our discussion.

DR. SMYTH.—I have been asked to speak on the sensitivities in childhood, their importance, early diagnosis, management and treatment.

Those of us dealing with the health of children have failed to be impressed by the frequency with which some problem related to sensitivity is encountered. Hardly a day goes by but some child is seen with a skin manifestation related to an obvious sensitivity, or as seems more likely a skin response in which the cause is not readily recognized. For this reason I believe it is the duty of pediatric departments to maintain allergy clinics in order to train properly the pediatricians of the future. This statement is not intended to invite controversy with those colleagues on this panel who are exclusively engaged in the study of allergy, but rather to state my position regarding educational policy. And, while I do not doubt that there are times when it is a relief to refer a troublesome patient to a specialist in the field of allergy, the fact remains that the pediatrician in intimate relation with his patients may have advantages and duties with respect to this frequently encountered complaint. In the matter of history alone the pediatrician is able to evaluate and clarify information which seldom is obtained from a limited number of interviews.

Besides its frequency, allergy in early childhood is important for the very reason of our rather limited understanding of it. In general it may be said that the disease entities in the adult are often confused by complications and that the pure entities seen in childhood give us the hope not only of earlier recognition, but also of preventive measures. This statement, however, implies an accuracy of diagnosis, which as yet I am unable to admit.

For clarity let us list the conditions encountered in young children: Urticaria, eczema, purpura, angioneurotic edema, asthma, and hay fever. First perhaps in frequency would come skin manifestations. More specifically I refer to the urticarias and the eczemas, or just eczema.

Regarding urticaria in young children, it is surprising how diverse the reports can be. Our experience has led us to suspect that a fairly large percentage of young children may have urticaria, but that this may be of a transitory nature and is perhaps less likely to be preceded or followed by any more serious allergic complaint. The large macular urticaria is usually transitory in that it disappears in the course of a few hours. Certain observations are, however, worth noting.

First, the response is often obtained with the initial feeding of certain foods such as shellfish or strawberries and much of its history is often influenced by the nature of the offending fraction. In our experience shellfish as a causative agent is likely to become more fixed, while we have seen the urticaria from strawberries fade out if the patient continues eating them. There is then the greatest response at the onset of the season and minimal response or disappearance by the end of the season. There is also to be seen the contrast between these two foods, that while cooking will often reduce or prevent the response to the fresh strawberries, no such alteration is obtained with the fish. Another observation worth mentioning is the digestive cycle causing an apparent tidal appearance or disappearance of skin lesions. For example, initiated by the ingestion of shellfish, the urticaria reappeared though in decreasing severity with subsequent meals. This evanescence,

somewhat like the course of serum sickness, is directly related to the absorption cycle in the digestive tract, and may point to methods by which it may be combated. The treatment and management of these types of urticaria differ accordingly, and our interest might well be directed toward the offender—not the patient.

I have implied without so stating that in recognition of the causal substance, this type of urticaria is understood best by history. This may be easily obtained by a diary and trial-and-error diet. As far as eosinophilia, leucopenic index, skin tests, etc., are concerned, I am not impressed.

I am willing to admit, however, that occasionally *Pulex San Francisco* has embarrassed me. I was much chagrined in the case of a doctor's child recently. The appearance of the lesion strongly suggested a food urticaria. However, the distribution was unusual, being peculiarly concentrated around the waist band. A few of the lesions had a central pinpoint hemorrhage. By that I mean the reaction was not confined to the immediate zone of the bite. By history the mother was also hypersensitive to fleas. Whether this is a case of placental transmission I would not attempt to answer. However, in the absence of major sensitivity the use of pyrethrum in calamine lotion was very effective.

Papular urticaria is the second type seen in children; here, too, I must confess that but for distribution and microscopic search for mites I have found scabies annoying in the differential diagnosis. And my most recent confusion in diagnosis was with regard to lesions—again in a physician's child—suggesting papular urticaria. Involvement of the mucous membranes suggested to others the diagnosis of chicken pox. A sister in the home and a ward in the hospital have to date shown no subsequent contagion, despite the usual ease of transmission of varicella.

The use of skin tests, eosinophile count, leucopenic index, etc., is of little value in this type of urticaria. It is a much more chronic condition and seems to have a slow appearance and disappearance time. As such even more careful sleuthing is required. Dietary trial and error should allow no changes in less than four days. Oats and orange pulp seem to be frequent offending foods. I have, however, seen some instances in which fats such as butter and bacon are apparently responsible; these latter foods are emphasized by Bray who goes further and mentions the seasonal summer occurrence, noted also in our clinic. Bray also reports eosinophilia which as yet we have not found characteristic.

Eczema of infants has been subject to repeated studies and various terminologies. As yet I am unable to be enthusiastic about the term neurodermatitis nor to predict with assurance those who will continue into adult life with involvement of the floor surfaces and those who will have a spectacular improvement toward the end of the second year. The skin of infants is notoriously tender. Eczema to me is a response to irritation; that irritation may be single or multiple. A peculiar number of instances are associated with sensitivity to foods in which eggs, milk, meat, or oranges are found by frequency likely offenders. However, few if any pediatricians would rely on dietary measures alone. We have all witnessed the remarkable amelioration in the condition when the use of ointments and restraint is not neglected. And I think we have also been parties to those trying cases which result in shopping for the final improvement, which brings gratification to the physician fortunate enough to see the baby at about 16 months or 2 years, when that certain spontaneous improvement occurs.

A few years ago I visited Scheer's clinic in Frankfort. He had a number of infants in the hospital with an eczematous appearing lesion involving the buttocks, which he said was eczema and his remarkable success was due to the use of Hydrochloric milk. To me the condition is none other than the ammoniacal diaper which we customarily treat by eradication of *B. ammoniagenes*, by bichloride and strong boric acid soaking of the diaper. Cooke showed very clearly that the bacillus could

be influenced by acid feeding, hence Scheer's results. The point I would emphasize, however, was that Scheer was sure that the eczema in which I was interested was of a similar nature, even though distributed differently on the body. Dr. Hansen of Minneapolis has likewise suggested that unsaturated fatty acid content of the blood is diagnostic and gives an important clue in the therapy of eczema. Visiting Minneapolis I saw several infants so treated with considerable improvement, yet such improvement may occur after hospitalization alone. For a similar reason it is suggested that the rationale of sobee may be of value because of fatty acid content. The German program, however, is for lowering the fat content of the diet. To me the diagnosis and treatment, the classification and therapy of causation of infantile eczema are far from settled. Eczema is a response to irritation, and the more the infants scratch, the more they itch. The irritation may come from food, contact with wool or silk, exposure to light, sudden changes in temperature, excessive soap and water, etc. Its diagnosis is not absolute.

The purpuric type of reaction is in our experience rare in children. I can illustrate the difficulty in this diagnosis no better than to mention an instance when Dr. Piness, the mentor of our children's allergy clinic, was visiting us. A 4-year-old child was seen by us and discussed in relation to allergic purpura. All agreed allergy was unlikely, yet under study we were able to induce or alleviate the symptoms by administration of orange with or without pulp. The skin tests, while faint, were interpretable because repetition showed consistent erythema only to orange.

I have had little experience with angioneurotic edema. In the one recent study the paternal history of allergy was strong. Another instance shall we say of germ plasm transmission? In this patient there is no doubt that certain foods aggravate the condition, but contributing factors such as excitability and/or the combination of foods are important in the production of response. Both parents are physicians and we have observed responses which admit no other interpretation.

In the second classification of symptoms we see the respiratory tract manifest sensitivities. While it is true that asthma and hay fever are found in very young children, the majority of recognized sensitivities in the young are still associated with skin manifestations. On the other hand, it must be admitted that a certain habit of mind has perhaps neglected the possible role of sensitivity for respiratory responses casually considered of infectious origin. An increasing number of instances without the premonitory skin manifestations have on suspicion shown a probable allergic nature. It is perhaps too early to predict, but I am of the opinion that rhinitis which looms so large in pediatric practice will warrant suspicion which should be directed toward an allergic study.

Osler I believe was responsible for suspecting the bronchopneumonia seen in the eczematous infant, as the initial onset of asthma. Pertussis has likewise proved dangerous for the subsequent course of such infants; nevertheless many instances of asthma in the older child may have little on which to trace the course of sensitivity. It pays, I believe, to anticipate probable asthmatic tendency, when infancy has been marked by eczema and food sensitivity, removing possible contact not only of the known ingestant offenders, but also of inhalants which by frequency are likely to be offensive.

In spite of such precautions there remains the possibility of sensitization to pollens, it being impractical to eliminate contact with these. We have seen pollinosis with either hay fever or asthma, or on the other hand with seasonal colds for which the pollens were responsible. However, it has been our policy, right or wrong, not to give courses of pollen injection unless the symptoms were marked.

With regard to the intestinal tract—the abdominal pain or colic of certain infants was early suspected by Schloss as of allergic origin. Associated with purpura or eczema, the implication is obvious. Eczema or asthma having previously been

seen to follow ingestion of egg, I am impressed with the cramps and diarrhea which may later characterize the response. Peanut which is less frequent in the diet may produce symptoms of this sort in the child otherwise without sensitivities. Will such a response persist into adult life? Who knows?

And another question. Is mesenteric adentitis allergic, rheumatic or both? We have seen relief with salicylates, none with epinephrine, but it has been present in several known hypersensitive children.

However, the lability of the intestinal tract in infants and young children is notorious. Colic, or bellyache, is far from rare and to suspect an allergic basis for symptoms readily produced by causes other than allergy, is I believe at this time dangerous. We have all seen the hypertonic infant with perfect nutrition screaming half the night spectacularly relieved with atropine or phenobarbital. We have also witnessed colic and diarrhea caused by an infection without a doubt. For this reason I am loath to suspect all instances of enterospasm or pyloric stenosis as allergic. With regard to its popular usage, I believe there is disrepute for the term, if we adopt it in lieu of the word "toxic" merely to screen our ignorance.

What is to be said concerning the initiation and the premonitory signs of allergy? Are we ready to grant Mayerhofer's contention that even in the neonatal period the transient rashes, etc., are allergic? If so, are we able to predict with some degree of accuracy the subsequent course the patient will follow? For my part I am unwilling to do so. There have been a few instances where as early as the first month I have told parents that I consider the rash suggestive of eczema, and have had the subsequent course typical of the milk-, egg-, and wheat-sensitive child, where eczema and later asthma have been related to these foods. However, not a little of my consideration was based on the family history, and, Dr. Ratner, in the instance that comes to my mind, the sensitivity was paternal. I inject this, not to disprove the possible placental transmission but to emphasize the hereditary factor, that is, the capacity to become sensitized.

I believe we are justified in guarding against likely offense in those children or infants suspected of sensitivity. On the other hand, I doubt if we are ready to advise against parenthood even where that hereditary strain is recognized. This you will recall was the suggestion of Glaser and Laudou.

We are still a long way from exact methods in allergy. I know of too few life histories to be assured that sensitivity in the young will be aggravated or alleviated by age. The marked lability of infants as a group affords no gauge for the reactions seen in older children or adults, and, while I think there is greater danger in the artful promise of outgrowing the disease, I have seen amelioration with adolescence far exceeding my hopes. All too frequently natural processes or at least factors beyond the knowledge or intent of medical treatment alter the nature and severity of the later manifestations. It would seem likely to me that, particularly with regard to skin responses, some tendency analogous perhaps to "street immunity" establishes some degree of protection. On the other hand, episodes such as infections may suddenly precipitate more violent responses than would have been predicted by the premonitory signs—a so-called minor allergy being followed by a major response. Perhaps the studies of Burky showing the ability of certain bacterial toxins to alter antigenicity will have more than casual bearing on the infection.

Now to summarize a few points concerning diagnosis, management, and treatment. So many of the symptoms we associate with allergy in infants may be produced by causes other than allergy that a diagnosis and the recognition of the causes are not easy.

The history of the family and a detailed account of the young child's responses are of the greatest value in the diagnosis of allergy. In very young infants direct skin

tests are notoriously unreliable, tending to develop perhaps from delayed to marked tests at about 4 months of age. The skin tests are decidedly helpful in older children but are not absolute. Eosinophilia is likewise fallible as a guide, having significance when positive, but its absence does not rule out sensitivity. The leucopenic index would appear to be of least value because of the normal fluctuations in the young child. There remains the detective work with trial-and-error diets and detailed diary follow-up.

On treatment I believe we are justified in suspecting the rashes suggesting eczema and the colic which may be associated with them. However, the treatment of eczema by dietary means alone is likely to be disappointing. Avoidance of certain foods, contacts, and inhalants, which are found offensive for many of these patients, as well as those suffering with asthma, is logical and perhaps preventive. Urticaria may be a transitory or minor allergy but it is not always easy to differentiate. In many infants there remains the role of nervous disposition occasionally seen to a marked degree in angioneurotic edema.

The very symptomatic treatments such as ointments and lotions for eczema, epinephrine and neosynephrine for asthma and hay fever, air filtration, etc., are of great value. Quite apart from the immediate relief so essential to medical practice these measures are in the same category with the rest of the program. To borrow a psychiatric term every effort should be made to break the pattern of response.

CHAIRMAN RATNER.—I am sure you will all agree with me that Dr. Smyth's survey is highly philosophical and yet he has offered many practical points of value. It is a pity that time does not allow Dr. Smyth to tell us more of the complexities of the eczema problem. Chevalier Jackson once said that "all is not asthma that wheezes," and after listening to Dr. Smyth's description of eczema we might apply this aphorism and say that "all is not eczema that itches." Dr. Smyth, you've stated that eczema is a response to irritation which comes from many sources, and I am wondering what your opinion is about the metabolic causes for eczema, whether you believe that certain types of hypothyroidism influence eczema, particularly in cases with delayed ossification.

DR. SMYTH.—I don't believe, Dr. Ratner, I could answer that. I have not been impressed with the theory that the thyroid had a direct relation to those youthful types of infantile eczema which we find with definite skin tests and in relation to some foods by trial-and-error administration.

CHAIRMAN RATNER.—I am almost in total agreement with everything you have stated, but I cannot let the remark about the hereditary factor versus intrauterine sensitization pass without comment. I regret that because of my work on intrauterine sensitization, the general impression seems to be that I regard this as the sole mode of sensitization in the young infant. We have found only about 30 per cent of our children who gave adequate evidence of that type of sensitization. On the other hand, I do not think that the child necessarily requires a family history to develop allergy. I believe with others that allergy or the capacity to acquire allergy is a universal attribute of the animal kingdom. I think that heredity may play some role, but it influences a rather small percentage of the children who actually develop allergy.

DR. SMYTH.—Of course, Dr. Ratner, you take us again into a realm of philosophy rather than allergy. I think in one of the allergy reviews I quote the Quaker "Everybody's allergic but me and thee, and thee is a little allergic." I think Vaughan's use of the term minor allergy also points to the fact that perhaps you are right; the animal kingdom has this general tendency, some in marked degree, some to a lesser degree; nevertheless, at least from a practical standpoint I would be

unwilling to neglect the importance of family history. I rather think that while granting placental transmission, Woringer's criticism of the wholesale acceptance, in view of the instances where the paternal influence was so marked, prompts one to keep a rather liberal point of view. It is true, even with careful histories, that there are plenty of instances where one cannot obtain a story of hereditary. On the other hand, sometimes I feel the history on allergy is an open book because you begin, and sometimes parents will say, "There was nothing like that in my family." At a later date when they understand it, they will come in with a history and you wonder why they held back because it is a beautiful story.

CHAIRMAN RATNER.—How do you explain, Dr. Smyth, those cases of individuals who react the first time they ingest milk or eggs? Do you have any explanation other than the congenital concept?

DR. SMYTH.—I grant you that this case may be due to a type of activity similar to serum sickness. I recall Dr. Piness' pointing out that some of the reactions that we get would be group reactions and that we might find some individuals reacting to pollens found only in the high Sierras, when you know very well they haven't been up there. In the matter of egg white there is something confusing in that to me. I have often wondered whether proteins of the larger molecular structure are multiples of albumin, and whether that accounts for the peculiar predominance of egg white which is something, I think, in a class by itself.

CHAIRMAN RATNER.—I am familiar with that viewpoint of yours, but after all egg white does have one of the smallest molecular weights of all the proteins. It is highly diffusible and it is an ubiquitous component of the average diet. For these reasons I believe that egg white is so common an offender. I do not think that we must put it in a class by itself, any more than any other albumin.

DR. SMYTH.—I still feel there is something peculiar about egg white in its activity, its frequency, and its violent peculiar actions, out of all proportion to the tests with other allergens. One of the earliest experiences that I have had (I think Dr. Piness remembers when I started with the intracutaneous testing) using in a known egg-sensitive child what I thought was a very weak solution of egg white; I injected the egg white solution intracutaneously and either hit a capillary or was, as Dr. Piness said, so unfortunate as to strike the one in twelve thousand, but at any rate that child had anaphylaxis; so did I.

CHAIRMAN RATNER.—Before proceeding with this discussion I want to remind the panel that we are to have a free, easy, and informal discussion, interrupting one another at any point; I hope that you will all join in that spirit. Those in the audience can write their questions and send them up to us, and we will try to answer them as time permits.

DR. PINESS.—Dr. Smyth, I want to ask you if there is such a thing as a minor allergy. If there is, what is it and how do you explain the cycle that follows?

DR. SMYTH.—In my experience a minor allergy as I see it is an urticarial response, for example, that is transitory, with no other developments—for example, transitory hives from strawberries. Patients may have them one year only, they may come up the first of the season, or they may have them for two or three years. I do not think that this type of patient develops asthma or of necessity has urticaria of the nature through life.

CHAIRMAN RATNER.—Do you believe that type of urticaria is allergic?

DR. SMYTH.—Well, it is an altered sensitivity which the majority of us do not show.

CHAIRMAN RATNER.—In what percentage of urticarias that you have seen in which you have been able to determine the etiology would you say that the etiology is determinable by skin testing? What percentage of this group do you believe is definitely of the so-called allergic type?

DR. SMYTH.—Of course, again you have raised the question of terminology. Let's forget terminology. I believe that the majority of these patients with urticaria have not skin tests which we can interpret, but I think that we have a cause and effect that are demonstrative by trial-and-error diet.

CHAIRMAN RATNER.—Do you believe that these patients do by trial-and-error diet bring out the etiology and that they are definitely food sensitive?

DR. SMYTH.—Some of them, yes.

DR. PINESS.—Would it be interesting for you to know that in a large series of urticaria patients, only 10 per cent were determined by specific tests or by guess, as it were, on the part of the patient and the family, due to some food, and that 90 per cent were due to drugs, the chief worry being aspirin and the second largest in the series being phenolphthalein. Has that been your experience?

DR. SMYTH.—We have some hypersensitive children, but I think, not so large a series as you may have, from which to draw conclusions. I still unfortunately remember certain ones in whom I think we have ruled out the possibility of drugs; now I would not leave you for a moment with a feeling of any satisfaction about our ability to diagnose and to understand these cases.

CHAIRMAN RATNER.—Dr. Piness, do you infer that drug sensitivity is not truly allergic?

DR. PINESS.—I believe it is a true allergic thing. I am not discussing the question of its being all allergic phenomena. I believe the drug sensitivities are definitely allergic, the best proof being the work of Landsteiner that it is possible to hook up body proteins with drugs, particularly the acting group and make them then result in drug allergy. Now it is very possible that is what happens in the aspirin group particularly, not impossible and probable with the phenolphthalein group. Many of the other drugs which produce these urticarial eruptions are, in the nature of, or are, alkaloids. But I am convinced that skin tests give very little information as far as urticaria is concerned, and I am certain that patch tests give no information because I have never seen as yet, a patch test with any drugs that are common, accepted causes of urticaria which has ever produced a similar lesion by their application to the skin. In the literature which has been reviewed by us recently, we found that of all of the men that have discussed drug allergies none ever reported a ways and means of discovering the etiology by these tests, or by any chemical tests of the excretions or the blood. So I say that we must assume that there is such a thing but we are not able to prove it by specific means.

CHAIRMAN RATNER.—I think we shall proceed with our discussion. Dr. Smyth has commented on the fact that the nature of the offending factor may differ in foods; thus, although heat may reduce the antigenicity of certain foods, among which are milk, eggs, fruit, berries and cereals, yet with others, such as fish, cooking actually enhances its antigenicity.

He has also indicated to you that while sensitivities may not be entirely limited to foods, even in the cases of infantile allergy, as has been the general impression,

foods do play a major role. Hence I shall call upon Dr. Rowe, who has contributed so much to our better understanding of the food allergy problem, to discuss its many intricacies, especially as related to childhood.

DR. ROWE.—Dr. Ratner and members of the section, I am very glad to be able to take part in this discussion this evening and I will proceed to give you some of the ideas that I have gathered according to Dr. Ratner's suggestion.

Why should my baby or child, or why should I myself, above all others, develop an allergy is a question which greets all physicians today. The best answer is that everyone tends to become allergic, but the tendency is heightened by heredity, that allergies due to inhalants, ingestants and contactants may develop at any time of life.

Now how does our food allergy develop in infancy? This has already been discussed in part, but I am going to have my little expression at this time. Usually allergy arises after birth, to foods following their addition to the diet. Intermittent feeding of a food may at times be responsible. The former practice of feeding a little egg white during the first few days of life until the breast milk appeared may have initiated some allergy in susceptible babies.

The same result probably arose from the temporary feeding of milk at birth. Thus if cow's milk in any form must be given during the first days of life, even though plenty of breast milk is soon available, it would seem advisable, particularly in babies with a strong family history of allergy, to continue small amounts of cow's milk until weaning. This same precaution should be taken against occasional feeding of vegetables, fruits, and other foods to subjects predisposed to allergy.

Overfeeding, particularly of one food, is another likely factor in the production of food allergy. If one remembers that allergy is essentially a protective response of the tissues to foreign substances, the origin of sensitization to a food fed in excessive amounts is not surprising. Moreover, food allergy may arise during digestive upsets or during acute illnesses in susceptible children.

The emphasis must be on the degree of positivity of the family history, for comparatively only few children or adults exist whose family history fails to reveal some evidence of allergy in its various forms; with marked evidence of food allergy in the progenitors, therefore, infants and children will be more susceptible to various disturbances from food allergy.

A similar tendency to develop manifestations of pollen or other inhalant allergies exists in the progeny of inhalant-sensitive parents. Also there is an inherited predisposition, in my experience, to definite manifestations of food allergy, such as gastrointestinal, cutaneous, nasal or bronchial symptoms. Asthma, eczema, nasal allergy, or migraine, or recurrent headaches certainly tend to run in families, also the tendency to become allergic to a specific food such as egg, milk, or even individual vegetables or fruits at times seems to be determined in part by heredity. Many instances of milk or egg allergy in three or four generations are recorded in the literature. Such specific effect of heredity, however, is not the rule.

From the practical viewpoint, if a definite history of milk, egg, or wheat, or other food allergy exists in the family it might seem wise to be cautious in the addition of such foods to the infant's diet. In the case of milk, evaporated milk, which Ratner has shown to be less allergic than other milk products, might be utilized. Or if milk allergy has been a great problem in the progenitors, a milk substitute like sobee, could be used entirely, with the gradual addition of minute and increasing amounts of denaturized milk, hoping that hyposensitization would gradually arise. This procedure fortunately should be rarely necessary.

Where egg allergy exists in the family or marked sensitization to other foods in the family is evident, egg may be excluded for a varying number of years. This is especially true when skin reactions to egg are present. When egg is finally added,

it should be given with minute amounts, gradually increasing it over a period of several months, according to evidences of any clinical reactivity.

Food allergy also develops from foods eaten by the mother during the uterine life, as demonstrated clinically and experimentally by Ratner. The one-cell membrane in the placenta is largely responsible for the passage of food allergy from the blood vessels of the mother to those of the child. If there is an inherited tendency to the development of a specific food allergy such as egg, the ordinary amount of such food eaten by the mother could lead to such allergy in the fetus. In cases in which such predisposition does not exist, overeating by the mother during pregnancy is probably responsible for the origin of specific food allergy in the fetus. One patient aged 20 years developed a marked allergic conjunctivitis whenever rice was eaten; her mother overate of rice given her by the Chinese cook during her pregnancy. The origin of such specific food allergies during fetal life as a result of chromosonal action, but not by food allergy transmitted through the placenta, must also be remembered.

How frequently it occurs, whether the actual sensitization is inherited or whether it is due to the predisposition to become sensitive to specific foods, is impossible to state with the present available knowledge. How much sensitization of the infant arises from food allergens in the mother's milk it is difficult to say. Food allergens in such milk, as demonstrated by Donnally, are present but in extremely small amounts; such small amounts of food allergens might lead to sensitization in an infant with a marked inherited predisposition to allergy to such food. If this tendency existed, however, it would seem that placental transmission of such food allergies would establish fetal sensitization. Moreover, before sensitization through breast milk is accepted, the possibility of previous feedings of small amounts of food, or the deposit of such food on the lips of the infant by kissing or by the infant's hands, which have touched that food, might in turn have to be considered.

We will now discuss some of the problems of food allergy after its establishment in the patient. After one sensitization to a food arises, allergies to biologically related foods frequently, though not necessarily, develop. One may be sensitive to all citrous fruits, or to orange and not to lemon and to grapefruit. Likewise allergy may be present to several or merely to one of the pit fruits. As marked fruit sensitizations continue, allergies to other unrelated foods may arise. In a few patients allergies to many or nearly all fruits unfortunately may occur.

Extensive sensitizations to practically all pollens are encountered, which indicates that allergy to a great number of foods of all types may also develop. Thus with the establishment of specific food sensitizations it would seem important to control them in order to prevent more extensive difficulty.

Food sensitizations vary in the degree of their resultant manifestations. There are many more mild indefinite results than severe marked disturbances and those mild effects may produce discomfort and inefficiency which need relief. The symptoms may arise rapidly after the ingestion of the food or may delay for a few hours or even a few days; they may appear only after repeated ingestion of the food for days or even weeks depending on the amount of tolerance existing to the food. Moreover, a refractory period in which desensitization is present often arises after a marked clinical reaction to a specific food has occurred. This explains recurrent attacks of asthma, every one to four weeks, or nasal allergy, headache, even though the food is eaten every day.

One food may produce asthma, other foods may produce hives, others may result in gastrointestinal symptoms in the same patients according to the location of the specific reacting bodies to the food allergens in the cells of the body. Manifestations of the food allergy tend to decrease or disappear during the summer months. Patients sensitive to wheat, milk, or eggs often can eat such foods from May until

mid-August or September without the asthma, nasal allergy, or eczema which arises from them during the fall, winter, and spring. A history of lessening of allergic manifestations during the summer months therefore should suggest possible food allergy.

Of great interest also is the fact that manifestations of food allergy especially are decreased, or may disappear when the patients go ten to twenty miles away from the Bay or coast line. Such nasal or bronchial allergy may disappear in one to three days in such territory only to reappear in a day or so on returning to the maritime region. This favorable influence is especially noted in the foothills or mountains of the Sierras here in California, or in the desert. Altitude is not responsible, since the benefit occurs in Death Valley, 300 feet below the sea level. It has been suggested that the mineral content of the air, being greater near the ocean, or that ionization of the air may explain this effect, but no assured explanation is at hand.

Uncontrolled pollen or other inhalant allergy may enhance food sensitizations which exist.

The statement that food allergy must always be studied with the possibility of inhalant, contactant, and to a less extent bacterial allergy in mind is important to emphasize.

Manifestations of food allergy at times gradually diminish or disappear, giving place to another symptom complex. Thus allergic dermatitis in infancy may be superseded by allergic bronchitis, asthma, or nasal allergy at the end of the second year. Recurrent vomiting or bilious attacks in childhood may resolve into recurrent sick headaches or migraine in the teens. Food allergy, however, rarely if ever disappears entirely and may remain potentially present without manifestations all through life.

A few comments will now be made on the diagnosis of food allergy. A dietary history often offers important clues concerning active food sensitization; all histories, whether of infants, children, or adults, and I may say for any medical condition, should contain this dietary information. In infants foods which are regurgitated, produce erythema or rashes of the skin or gastrointestinal symptoms must come under suspicion. In them, as in children and adults, foods that are disliked or produce definite disturbances of skin, nasal, bronchial, or gastrointestinal tracts must be suspected.

Such history may be more important than skin testing, but skin testing should always be done. Skin reactions, especially by the scratch test, are often negative to foods causing definite allergy. Skin-reacting bodies to such foods are absent, the sensitization itself being confined to the cells of the shock tissues whether in the lung, the nose, or the gastrointestinal tract. Positive reactions may only indicate the potentiality or may be nonspecific in nature and must therefore be checked by clinical trial or by a definite history of allergy thereto. The patient may give a few skin reactions to foods some of which are productive of allergy and may fail to react to other foods which cause equal or greater difficulty.

More reactions are often obtained with the intradermal tests with food allergies than with scratch tests. Here, however, a greater number of nonspecific reactions tend to arise and negative reactions to allergy-producing foods still may occur. Thus for the diagnosis of food allergy in childhood, as well as in adult life, diet trial, at times with several types of elimination diets, often over a period of weeks must be utilized. Such diet trials, however, are absolutely contraindicated if any nutritional damage is likely.

Food allergy in infancy probably produces more manifestations in the gastrointestinal tract than in any other tissue. Regurgitation, colic, distention, diarrhea, and feeding difficulties often may be due to mild or more definite allergies; spasm

of the pylorus has been reported as due to food allergy in certain instances, and it is possible with its continuance that actual stenosis might arise.

How many of these gastrointestinal symptoms are due to food allergies or how many arise from impaired digestive function is impossible to tell. Deficiencies in hydrochloric acid or digestive ferments or in the peristaltic action in the intestines themselves may account for a definite number of such symptoms. Food allergy is often responsible, however, and must be constantly in mind.

After infancy food allergy continues to affect the gastrointestinal tract. Canker sores so frequently due to food allergy are probably urticarial or small Arthus-like lesions. It is entirely possible that such cankerlike lesions may occur in the stomach or duodenum, and, when increased by the acid and digestive ferments, they may develop into peptic ulcer.

Localized allergy in the stomach, intestines, and colon in childhood producing disturbances in peristalsis and digestive function may result in coated tongue, belching, regurgitation, distention, nausea, vomiting, cramping, abdominal soreness, spasms, irritable bowel, mucous colitis, diarrhea, constipation, rectal spasm, and irritation. Pruritus ani at times is due to allergy and may result in a localized eczema.

Recurrent vomiting often producing acidosis should always suggest food allergy. A refractory period develops after such an attack with a gradual building up of the allergic reactivity over a period of days or weeks as an explanation of such interims of relief. Such vomiting occurred in a five-year-old boy whom I recently saw and resulted in acidosis associated with a high blood sugar. At first diabetes was suspected, but with the recurrence of vomiting three weeks later allergy was assumed; with the use of trial diets no difficulty occurred in the last seven months except on one occasion when milk was taken against orders.

Anorexia, especially when mild or severe gastrointestinal allergy is present, should suggest food allergy as one possible cause. It also occurs when food or another allergy productive of nasal, bronchial, and especially of toxic symptoms is present.

Perennial nasal allergy, allergic bronchitis, or recurrent asthma is frequently due to food sensitizations at all times of life especially in childhood. As noted above, such symptoms are helped by inland residence and by the summer months. Sneezing, nasal congestion, and watery discharge without definite itching of the nose should suggest food allergy. Inhalant allergy more often results in itching. Opaque antra often arise from sinusal allergy, especially to foods. Eosinophiles are usually found in the nasal secretion. Mucous membrane edema and at times polyps cause the opacities. Thorough allergic study and prolonged treatments are imperative; opaque antra in themselves are never an indication for surgery.

Bronchial asthma arising from food allergy in childhood is usually indicated by allergic reactivity in the nose and sinuses for one or two days, giving the impression that a cold produces the asthma. Such nasal symptoms, however, actually are not due to infection. The secretions contain eosinophiles and not pus cells. They are the result of allergic reactivity which starts in the upper part of the nasal bronchial mucosa and localizes in the bronchial tissues after the first day or two. Since more attention has been paid to food and associated inhalant allergy as a cause of such asthma, and bacterial allergy has been relegated to its rare and infrequent role, results have been most satisfactory.

In the skin, food allergy is a usual cause of urticaria and angioneurotic edema. Fruits should always be suspected in urticaria and if elimination diets are used to study such cases, fruit should be excluded. Eczema or allergic dermatitis in children, and especially in infants, demands consideration of food allergy. As age increases, the inhalants must receive increasing study, and contactants as a cause of sensitizations must be recognized. In allergic dermatoses information derived from history, skin reactions and the results of diet trial, environmental control, and hyposensitization therapy in varying degrees must be used to determine finally

the etiological causes of the difficulty. Food allergy as one cause of allergic purpura and mucous membrane bleeding must also be mentioned at this place.

Other manifestations of food allergy alone or associated with inhalant allergy must be kept in mind. Allergic conjunctivitis, corneal ulcers, and other less frequent ocular disturbances occur. Genitourinary tissues are not exempt. Recurrent vulval edema, congestion, itching, eruption, associated with fever and vomiting occurred in two children in my experience. Enuresis from uncontrolled food allergy has been recorded and observed in my work. Frequent and urgent urination with negative findings in the urine may be due to bladder allergy, which occurs occasionally in adults. Fever arising from food allergy has been studied by several students, emphasizing the consideration of allergy as one cause of the so-called idiopathic fevers.

Finally, uncontrolled allergy, especially to foods, leads to irritability, nervousness, restlessness, incorrigibility, wakefulness, nightmares, and other associated evidences that allergy directly or indirectly may act detrimentally on the brain and the nervous structures of the body.

In considering food allergy and other types of allergies as a cause of any symptoms, it must be stressed and emphasized that most careful physical examinations, laboratory tests of all indicated types must be done to recognize and rule out any diseases or pathologic states other than allergy that might be causing the patient symptoms.

CHAIRMAN RATNER.—Dr. Rowe, your discussion was so thorough and complete that I am sure that your remarks will give rise to many questions. I know that your task was the discussion of food allergy, but I had the feeling as I listened to you that probably food allergy was stressed a little too forcibly. We have had a peculiar reaction recently in evaculating our cases and find that infants who had food sensitivity even with eczema, as Dr. Smyth has brought out, or urticaria or rhinitis, may actually be sensitive not only to food, but also to inhalants and contactants. It seems to me that undue stress laid on food alone might tend to give us the impression that the finding of the food factor may solve the problem, but I doubt it very much, although I realize that food is a very important factor.

DR. ROWE.—I thoroughly agree with you, Dr. Ratner, about that; I believe though that in infancy and in the first few years of life food sensitization probably is more frequent in relation to inhalants than it is as years progress, and I believe that the criticism of the emphasis on food during infancy and in the first year or two of life is possibly well taken.

I took the occasion, however, in my discussion—I might have made it a little more definite and I realize that I was talking about food allergy all through the paper—to point out the fact that food allergy should never be considered alone—that inhalant allergy should always be kept in mind. And as I go along with my work I am in full accord with you that inhalant and contact allergy must always be given due consideration.

CHAIRMAN RATNER.—Dr. Rowe, I realized that that was your opinion and I just wanted to emphasize it. You brought up a question that is of particular interest to pediatricians, namely, the dangers of giving raw egg white or raw milk during the neonatal period. You emphasize, however, that these infants should not get this type of food if they have a background strongly suggestive of hereditary allergy. I for one believe that no infant should get these highly allergenic foods, irrespective of their heredity because of Schloss's work which showed that in normal and athreptic infants unchanged proteins do pass the intestinal wall in the native state.

DR. ROWE.—I believe that that is a point which is well emphasized; however, I still feel that many of these food sensitivities develop in children who have a strong inherited tendency and that there is in certain of them an inherited tendency to develop specific sensitizations to definite foods. I believe though in pediatric practice, with which I am not acquainted to any degree, that the custom today in the early days of infancy is not to feed uninterruptedly these foods that Dr. Ratner spoke about.

DR. W. A. McGEE (RICHMOND, VA.).—Dr. Rowe, I should like to mention two or three things. Do you find with the feeding intervals at three days when you have a child that is apparently allergic you can often steer clear of that offending food? I am not talking of inhalants. Have you found when you put them on the milk substitute you mentioned, if you have used it, clinical evidences of olive oil sensitivity? I have recently run across three of them that could not take milk and could not take olive oil, ruling out one of the most available milk substitutes. The other is that in an allergic child I feel the use of multiple cereals, multiple fish oils, and vegetable soups is definitely contraindicated.

DR. ROWE.—I am not in a position to discuss the practical aspects in feeding in the early days or months of infancy because I do not do any of that at all; but it seems to me that if milk has to be given and breast milk is not available, it would be a great mistake to stop the milk—if it is decided later on to use breast milk for a period of time, and particularly if there is a marked history of allergy in the family. In other words, if the breast milk is to be given in place of cow's milk that has been given previously, I would suggest that small amounts of cow's milk be administered every day or two or every four or five days to possibly prevent any establishment of future milk sensitivity.

About these other suggestions that the doctor made, I believe that it is entirely possible when a complex food like sobee is used, it must be remembered that sensitization to any one of the ingredients might certainly exist. How often it occurs, of course, I think is uncertain. I believe it is rather rare.

CHAIRMAN RATNER.—Dr. McGee, with reference to your remark about the multiple foods of infancy I see no objection at all to giving multiple foods provided that those multiple foods are denatured by heat. For example pablum, which has a multiplicity of cereal ingredients, has been shown experimentally to be quite free of antigenicity, and there is no reason at all to eliminate the multiple foods so long as they are heated and not given in a raw state. I think this is a point that is important to pediatrics practice.

DR. McGEE.—Dr. Ratner, that might be true experimentally and may sound true, but practically, I have seen many an infant who could not take it. We are not talking of skin tests, and it comes home to my own child.

DR. SMYTH.—I do not know whether I am just timid or reactionary, but when I listen to Dr. Rowe, the list of complaints from which you get an allergy I think you are very enthusiastic. I think it is perhaps almost dangerous to leave the impression, for example, that migraine is solved on an allergic study. Migraine to me is a riddle. If you solve it—God be praised. I think of the vomitus; how do you account for the frequency with which we find ketonuria preceding the episode of vomiting? There surely is a metabolic picture at least in some of them which deserves recognition fully as much as an allergic study.

I noted you mention also the dislike of certain foods. Have you not encountered certain individuals who with known sensitivity, even adults, will partake of shrimps when they full well know the symptoms they will have; they do not get edema of the glottis, and they like the sensation of eating the forbidden food.

This is perhaps baiting you, among pediatricians. What would be your feeling about the eczema of the breast-fed infant? You mention Donnally's work, but it seems to me the technique that Donnally used is not above criticism. He was injecting curds of milk, and I think there is some real room for controversy about that.

Dr. Ratner mentioned Schloss's thesis, which I think is a fine one; nevertheless, the work with intestinal absorption has shown that even the normal individual will absorb protein from the intestinal tract and show a positive skin test by the Prausnitz-Küstner technic, so that that may be a normal mechanism in part. In fact, I wonder if our physiology is not perhaps erroneously worded that it leaves us with the impression that even in the normal gut certain types of protein may be absorbed and altered.

CHAIRMAN RATNER.—Dr. Smyth, there has been a great deal of discussion about the factors which influence heredity. Your bringing up the point of the work of Schloss and calling it a normal phenomenon leads me to express the following idea. Do you not think that allergy is a normal physiologic type of reactivity? There is no reason to suspect that heightened reactivity is not a normal physiologic capacity of the animal kingdom.

DR. SMYTH.—It seems to me that that suggestion, as well as Lippard's work, more recently, which is certainly aiming in that direction, and also the statement that allergy may be a protective reaction, is today one of the controversies from a theoretical angle that is far from settled. I refer to Arnold Rich, particularly working with tuberculin, who challenges very definitely the idea that perhaps it is an awful price to pay for the protection that certain individuals have.

DR. PINESS.—Dr. Rowe, I should like to ask in your experience, which is long and very wide, how many cases did you actually see in children from the age of one year, or under one year, to ten years who have been actually sensitive to foods and foods alone?

DR. ROWE.—It is my impression that quite a number of patients have in childhood and in infancy food sensitizations without actual clinical manifestations of inhalant allergy. That is a statement, of course, which could be modified by reference to the records, but I think that there are a great many children who are sensitive to food alone.

DR. PINESS.—That statement, I take it, is based on both skin test and elimination diet. Well, on the basis of skin tests alone how many have you observed? Up to 1930—was that when elimination diets came up? No; 1927. Your reports were formerly on the basis of skin tests?

DR. ROWE.—Well yes. In 1925 I reported—

DR. PINESS.—Well up to 1925, if I remember correctly, you reported that some 95 per cent cases were skin sensitive; we are not speaking of clinical sensitivity for the moment. And in that 95 per cent how many were sensitive to foods and foods alone by skin tests? And since then, if you know that?

DR. ROWE.—I cannot remember.

DR. PINESS.—Well, would it not be interesting to you to know that in five thousand children alone, we found only 1 per cent were sensitive to foods and foods alone, and the others were divided up into groups sensitive to pollens alone, epidermals alone, and then the multiple group. You are, I think, in accord with most of us that multiple sensitivity is the common type of sensitivity, is not that right?

Well, under those circumstances which do you believe is the most common food that one is sensitive to?

DR. ROWE.—Well, I have never really gathered statistics which would give me any basis to discuss that, but I think that milk is unquestionably a very common one, and egg; I think many of the fruits are equally frequently causative. Of course, I believe that many of these food sensitizations as demonstrated by skin tests are not associated with clinical sensitivity. Just because a patient gives a positive skin test, particularly by the intradermal method, does not mean that the patient is clinically sensitive to that food.

DR. PINESS.—Anticipating that from you I brought with me some facts that I think are rather interesting. In a thousand children of consecutive cases at the Allergy Clinic, Children's Hospital at Los Angeles—these children are clinically sensitive and not skin sensitive cases, and in them we were able to reproduce the facts at will—we found the following: Wheat, which you take to be one of the chief offenders, was fifty-fifth in that list; milk was forty-second; orange was fourth and of the cereal group in which we are all interested, particularly the pediatrician, barley was the most common. The most common fruit was orange, and the most common vegetable was lettuce, which was fifteenth; egg white was fifth. Now the others—white potato, for example, which is commonly used, was fortieth; and an interesting fact was that cod-liver oil was sixty-second on the list. One hundred seventy-three in one thousand children were sensitive to cod-liver oil. I think that is rather interesting because I do not believe that skin tests should be minimized to the extent that you suggest. I believe that skin tests have a real value and that value is dependent upon the clinician's ability to correlate a skin test with the clinical history. I think that the advantages of that are much greater than one obtains from elimination diets. It was rather interesting too in this whole group of cases in Southern California, we were able to get a higher percentage of children with pollen reactions than we did with foods. Orris root, which we are all discussing, was eleventh in the list of inhalants, and it's rather interesting, too, from our observation and from asking the mothers bringing children to the clinic the type of powders they are using, that very few of the powders these days contain orris root. I should like to have you answer how you can reconcile yourself to the elimination diet, disposing of such a report as this one. It seems to me illogical on the basis of scientific studies to accept the elimination diet as a substitute for such work as this.

CHAIRMAN RATNER.—I knew that there would be a very lively discussion. I feel that Dr. Rowe has some justification for his stand and that Dr. Piness is somewhat justified in his assertions. It seems to me, however, that the most important thing to be gathered from this discussion should be the fact that foods and foods alone play a minor role in the sensitivities of childhood, even in the very earliest instances, as Dr. Smyth has brought out and Dr. Piness has emphasized. It seems to me that no method as important as the skin test should ever be discarded; it is entirely too important and we should use all the methods available.

DR. PINESS.—Dr. Ratner, I did not want to give the impression that Dr. Rowe advocates the discarding of skin tests because he emphatically states in his paper that both systems should be correlated. My experience has been, and I believe, that there is a greater specificity to skin tests than there is to the elimination diet.

I should like to ask Dr. Rowe just one other question and that is on what he bases his theory that cases of asthma, I take it they were inhalant allergy, were better in the summer and might be due chiefly to foods.

DR. ROWE.—That is largely true experience, Dr. Piness, experience that I have gathered through a period of fifteen years of study. I am absolutely confident that most—many of these patients who have asthma or nasal allergy due to specific food sensitizations—are better in the summer than they are in the winter, and they are also definitely better when they go inland away from the bay region. There is not any question about that from my clinical experience, and after all clinical experience, as you all know, is a great deal more valuable in many instances than laboratory tests. I am perfectly willing to recognize the value of the scratch test or the skin test for foods, but I feel that with the intradermal tests that Dr. Piness uses there are a great many nonspecific irritant reactions that may indicate potential allergy that is confusing. When Dr. Piness gets a positive reaction to a food, he certainly has to check it up with a clinical trial in order to prove its worth. I feel really that trial diet modified by such reactions that are definite by the scratch test is about the best method that I have been able to work out through a period of fifteen or twenty years' effort in the study of food sensitizations.

CHAIRMAN RATNER.—Well, I think we all realize that there is a difference of opinion. I am going to ask Dr. Rowe just one more question. Am I wrong in assuming that you would have us believe that food allergies rarely if ever disappear?

DR. ROWE.—I think that the potential food sensitizations may continue. You cannot be absolutely sure that they disappear entirely. They may be potentially present for a long period of time.

DR. PINESS.—Dr. Ratner, since you have asked another question I think it my privilege to ask one too. I would like to ask you, Dr. Rowe, how would you prevent a child from acquiring a new food sensitivity, assuming that he is food sensitive? Pediatricians would like to know.

DR. ROWE.—Well, I think that overfeeding is important, as I have stated in this paper. Overfeeding of foods is an important thing to guard against, and certainly you have to be very careful about the way foods are fed during a digestive upset, particularly those affecting the gastrointestinal tract. Those are I would say the main ways.

DR. PINESS.—I would like to suggest a better and more simple method, if it is in order, and that is this: I believe that the easiest way and the most efficient way to prevent food sensitivities, that is the acquisition of new sensitivities, is by diversifying the diets. That is a very simple and very pleasing way for the child. I have found in my experience that feeding a child the same thing all the time is a very easy way to acquire new sensitivities.

CHAIRMAN RATNER.—I believe the suggestions of Dr. Rowe and Dr. Piness for the prevention of food allergy are both good.

There have been some questions from the floor and we will attempt to answer some of them.

DR. SMYTH.—The question is: How early may raw egg-yolk be added to the diet? Well I shall answer it in part by saying that at the New York Orphanage a number of years ago they had this formula—which I think they included for infants as young as two months—raw egg-yolk, lemon juice, and milk. To my knowledge they did not encounter a very high percentage of unfortunate reactions, but I think that if you are dealing with a nonallergic infant I would still be inclined to use hard boiled egg yolk crushed with a fork and avoid the egg white. It is true, however, that in quite a number of instances egg yolk can be incorporated into a formula, especially in an anemic undernourished infant, and little or no diffi-

culty will be encountered. I would be guided, I think, entirely by the patient, that is, if there is a marked allergy or sensitivity I would be inclined to avoid the raw egg yolk.

CHAIRMAN RATNER.—A question: Did Dr. Ratner say pablum does not cause allergic manifestations due to its having been heated? Is it not true that the individual sensitive to wheat is not able to eat cooked wheat bread? Now that's a very significant question. Pablum, as you know, has been heated to an extremely high temperature in the presence of moisture, about twenty-two pounds of pressure for quite a while. When proteins are heated in the presence of water at a high temperature they become denatured. The reason bread is not denatured is simply that bread is baked in an oven not in the presence of moisture —the outside of the bread comes in contact with about 500° F. and the inside of the bread with about 200° F. Experimentally we have found that guinea pigs sensitive to raw wheat can be killed by an extract made from wheat bread, but guinea pigs sensitized to raw wheat will survive an injection of pablum.

DR. SMYTH.—The statement: I use a great deal of powdered protein milk, due to its low albumin content. It is used successfully in milk-sensitive babies. What is your thought?

We have used the 2 per cent dried milk in the form of dryco which I think Dr. Ratner would tell us was equally altered in its reactivity along with evaporated milk.

CHAIRMAN RATNER.—Dr. Smyth, experimentally we did not find that dryco was altered. It is prepared by heating on a hot plate for a few seconds, and apparently this dry heat to which it is subjected does not change it antigenically. No protein is denatured by heat in the absence of water. On the other hand, evaporated milk is altered or denatured in the heating process to which it is subjected because of the presence of moisture.

DR. SMYTH.—Well then, Dr. Ratner, what is your opinion of this commercial protein milk? Have you any comment?

CHAIRMAN RATNER.—Lactalbumin is the most frequent offender in milk. I should say that powdered protein milk which has a much lower content of albumin than dryco might very well be used with good results in milk-sensitive children.

DR. ROWE.—The next question is: Did I understand you to say that you have observed all manifestations to food allergy to have a seasonal incidence?

It has been my experience that most of the manifestations of food allergy, as I have observed them, tend to be worse during the winter and particularly during the spring months of the year. That they seem to be better between April 15 or around there until about September 15.

DR. SMYTH.—The question: Please explain teething rash. It is a very convenient term. I do not know that it is always as easily explained. I think earlier in my discussion I said that the skin of infants was notoriously tender. We have seen instances in which about the time of teething a tendency for rash appears with increased tension. There seems to be an association, but that it is necessarily allergic I, for one, am not ready to state.

DR. PINESS.—Embarrassing question No. 1: If skin tests are valuable, how do you explain a child with no reaction to skin tests in whom symptoms to foods occur?

That is not very difficult to explain because after all no one contends that skin tests are 100 per cent; they are not infallible. On the other hand, skin tests that

are negative may be due to certain other factors. One, the antigen may not be active; two, the child may be in an anti-anaphylactic state. I do not know what it means. It may be a period when the skin is not reactive. And those of you who have done skin tests have observed, no doubt, that a child who has been tested once and gives 100 per cent negative reactions may come back in a month and give a very specific reaction. I think skin tests cannot be condemned on the basis of one child, or even the 24 per cent of children who are not reactive to skin tests, but it is a fact that many of these children will react on second testing.

DR. SMYTH.—Question: If the thyroid has no place in eczemas how do you explain the disappearance of eczema following the administration of thyroid gland?

I have seen eczema disappear without thyroid gland. I have seen thyroid gland used in the process called the treatment of its edema, simulating thyroid myxedema. I have seen eczema disappear in a sort of a profound diarrhea, only to reappear again when the fluid was re-established. It seems to me that the question involves some discussion of thyroid and its place in our therapy. There are some of us who feel that perhaps it can be overdone.

The second part of the question: If eczemas are a reaction to irritation, how do you explain the metabolic or constitutional differences between susceptible allergic individuals and normal ones? I am still looking for an explanation myself. Another question: What food should be avoided with the infant, allergic or non-allergic? Well, that would be open to discussion. Perhaps it varies with the section of the country, but I think perhaps strongly spiced foods and excessive use of stimulants, pickles, and a lot of indigestibles.

In general, the question is too broad to be specifically answered. Do you think of any answer? How would you think of that question?

CHAIRMAN RATNER.—Well, I think the question of what food should be avoided might be answered by stating that it is my belief that we would not have much food allergy if infants were fed denatured foods, provided an adequate amount of vitamin C were incorporated into the diet. It seems to me, for example, that the advent of evaporated milk is fast destroying the need for our skill as expert infant feeders, because practically all infants do well on evaporated milk. The application of this principle of heat denaturation to other foods in the infant's diet is a reasonable prophylactic measure.

CHAIRMAN RATNER.—Dr. Shaw states, "All children are allergic, at least that is all when given antigen parenterally. Is not the capacity to absorb unchanged protein a fundamental defect, the capacity to react to protein so absorbed being relatively universal? This better explains the mass action effect of the ingestion of excess amounts of food."

The question is really a good one, and Dr. Shaw answers it. His first statement, I presume, means that most children will develop serum sickness if given horse serum. I agree with him that the mass action of proteins coming in contact with normal membrane barriers accounts largely for the inception of allergy in childhood. We must accept the fact that serum sickness is truly an allergic phenomenon and does not differ basically from any other allergic phenomena we have been discussing.

The next question: Is it your impression that the frequency of allergy in infancy is the price paid for artificial feeding instead of breast feeding? Is not allergy less frequent in European clinics with 100 per cent breast fed infants? I cannot answer that question categorically. We do see allergy in the breast-fed infant, and I imagine that, when things clear up in Europe and some of our American allergists go over there, they will find plenty of allergies.

The next question raised is a rather interesting one. The doctor proposes a change of cereals, vegetables, and fruits on alternate days, and he asks what we think of this as a practical manner of feeding a baby. A diet consisting of a great variety of foods in small quantities and partially denatured will to a large extent eradicate food allergy, I am convinced.

CHAIRMAN.—I knew that Dr. Rowe's paper would arouse a great deal of discussion but didn't think it would take up so much time. I am sorry, therefore, that I will have to ask Dr. Piness who will continue our discussion to try to shorten his remarks. There are few men who know as much about the problem of rhinitis or hay fever in childhood or who have had any more experience than Dr. Piness.

DR. PINESS.—I came prepared to make my discussion a very short one realizing that I was coming so late in the program. Very few disorders of infancy and childhood are observed so commonly by the pediatrician as is allergic rhinitis. The reason for this is not hard to see. Mothers are well aware of the fact that coryza is the most common harbinger of evil at this age, and at the first sign of a running nose the pediatrician is consulted. Since coryza is also the most common symptom of allergic rhinitis and is also the most persistent and most frequently recurrent, we find sufficient justification for the statement made that there are very few disorders of infancy in childhood which the pediatrician observes so commonly. Because allergic rhinitis often foretells future frank hay fever and bronchial asthma and because it is a means of identifying the allergic constitution, it is important that the pediatrician be prepared to recognize this condition early in life so that the proper measures may be instituted to prevent the characteristic complications, and sequelae that result from the untreated allergic constitution.

How common then is the allergic constitution? The final answer is not yet determinable. In this regard it is interesting to note the various studies made on the incidence of allergy by the various workers in different sections of this country. An analysis of all the reports indicates a considerable similarity in their findings. Rowe in the study of 2,000 students in the University of California reported 35 per cent gave a positive family history and 33 per cent gave a positive history of having had or having some form of allergy. That is rather high. Vaughan surveyed a community of 508 individuals in which 60 per cent had some minor form of allergy (I contend again that there is no such thing as minor allergy because it is a constitutional disease and it is quite the same). Service made such a survey in a city of 35,000 population, using the sampling method according to economic distribution. He studied 1,000 families, whose total comprised 3,500 persons of all ages. He reports 44.9 per cent of the families surveyed had some form of allergic disease, and that 19.68 per cent of individuals in the general population had some form of allergy.

A positive history of heredity was elicited in about 32 per cent of these cases. This is considerably less than had heretofore been found by other writers but is quite in line with our own observations, resulting from a study made in Arizona of two communities with a total population of 4,000 persons, of whom 30 per cent gave positive histories of heredity—which at the time we thought to be lower than was to be expected. It would seem that heredity does not play a great part in determining how long an individual must be exposed before developing allergic symptoms. The consensus is that allergy in its various forms has its onset most frequently during the first decade of life. In a study made by us of a series of about 4,500 individual cases, 1,489, or 32.4 per cent gave a history of onset in the first decade of life, which is quite in line with the findings of other writers.

Rowe is of the opinion that food is responsible for most allergy during the first two years of life, inhalant allergy gaining increasing importance after that first year. We agree to the importance of foods as a factor during this age but wish to emphasize the importance of inhalants, particularly the environmental group, as being equally important in that exposure to them is equally as great as that to foods, perhaps more so. A consideration of this fact will result in more etiological information and better results from treatment. Hill reports observations in accord with our own.

Allergic rhinitis may be acute or chronic, it may be seasonal or perennial. It is a recurrent and often constant disturbance, and it is not infrequently considered as a repeated or persistent acute upper respiratory infection. The symptoms are characteristic. The acute attacks have a sudden onset, intense itching in the nose, eyes, ears, and pharynx, sneezing with a profuse discharge of serous fluid which, if the attack continues, becomes mucoid. There may be lacrimation and photophobia. The nose becomes completely or partially obstructed and usually symptoms subside rather acutely. Examination of the nose reveals usually an edematous congested, turgescent, mucous membrane with hypertrophy and edema of the turbinates. All nasal membranes have a characteristic bluish-white to deep pink color. The conjunctiva is usually edematous and has a granular appearance. This type is usually due to inhalants, and when seasonal, particularly during the summer months, is invariably pollen sensitivity. On the other hand, acute attacks that are not related to season are usually traceable to some environmental factor, such as insecticides, cosmetics, animal epithelium, and occasionally foods of the seasonal type.

The chronic and perennial types are characterized by recurrent daily symptoms chiefly occurring in the morning upon arising or upon retiring at night. Frequently the mother will observe similar attacks occurring when the child is put down for the afternoon nap. Here the symptomatology differs somewhat from the acute types in that the patient is usually free of symptoms the greater part of the day, symptoms are not as severe, but nasal obstructions in varying degrees are more or less constant. Examination of the nasal mucous membrane reveals a pale, boggy, water-logged, chronically turgescent mucous membrane, the chronic edema resulting in polyp formation on the turbinates and in the sinuses. Removal of polypi is disappointing in that they recur almost as rapidly as removed. In the pharynx there is a marked redness with hyperplasia of much lymphoid tissue in the lateral and medial positions. When the tonsils have been removed, much lymphoid tissue is evident on the pillars and on the fossae. The latter may be mistaken for tonsil regrowth. The diagnosis of allergic rhinitis should not be difficult and must not be missed, particularly when the above facts as to clinical history, symptomatology and pathology are known. Additional aids in making the diagnosis are a study of the nasal cytology, making smears from the nasal secretions, staining with Giemsa stain and noting whether or not eosinophilia is present. I refer to the work of Hansel who through his studies of nasal cytology has given us much information on the subject.

While blood studies are helpful, the presence of eosinophilia is not conclusive evidence of allergy; but in the presence of a positive family history, a story of having some other form of allergy, and a clinical history suspicious of allergy or a history of known allergic sensitivities, should be considered seriously in helping to establish a diagnosis.

Etiology of allergic rhinitis regardless of the type must of necessity be due to allergens, the nature of which we believe to be protein, although substances non-protein in nature are known to produce it, and by means of skin testing one may in the majority of cases determine it. Time and space do not permit, nor is it necessary because of your familiarity with the procedure, discussion of the various techniques and methods of skin testing.

Much valuable information and considerable help are obtainable by eliciting certain facts in the clinical history, particularly such information as time of onset, relation of season, duration of symptoms, frequency of attacks, environment, noticeable factors that precipitate attacks—such as foods, domestic animals, cosmetics, certain portions of the home, and hobbies that might be factors, too.

Foods alone as the cause of allergic rhinitis, in my experience, do not occur as the etiological factor as often as some writers would lead us to believe. Our observations, particularly in a child with chronic allergic rhinitis, show that there is usually multiple sensitivity. While on the other hand, in the seasonal type, particularly that occurring in the summer months, the symptoms are usually due to pollen. Those having their severest season during the cold months are usually due to environmental allergens, such as wool, feathers, etc., while the perennial types who find no relief either by moving from place to place, or through seasonal variations are most likely to be due to food or allergens from the environmental group.

I wish to stress the point that skin tests are not employed to make a diagnosis of allergy but merely to confirm the diagnosis made by assisting in determining the etiology. They are not infallible, and are only of value when they can be proved clinically as well.

Since we are dealing with a constitutional disease, possibly of hereditary nature, at least predisposition to acquiring sensitivity, one must not make unwarranted claims for cure but can assure the patient's family that relief from all symptoms is possible, the degree of freedom from symptoms depending upon the ability to eliminate from the diet or environment those substances to which the patient is clinically as well as skin sensitive and on the complete cooperation of the patient and parents. This cooperation is also necessary in the pollen-sensitive individual in whom relief may be obtained only by persistent treatment with specific pollen antigens over a long period of time.

One must not consider all positive reactions as being the cause of the present symptoms, but they must be considered as potential factors either in the past or perhaps in some future time.

The treatment of allergic rhinitis then resolves itself into the removal of the offending allergens by eliminating the offending food from the diet, by removing from the environment the offending substances, and, if this is impossible, to make and treat with an antigen prepared from those known offenders. In the pollen-sensitive patient, prepare antigens from pollen and treat with these, but only after a careful study is made of the patient's history and after it is considered with regard to the reacting pollens that the patient may contact. To be able to accomplish this, it is necessary for the clinician to familiarize himself with the flora in the vicinity in which he resides, as well as the pollinating seasons. We are of the opinion that the majority of children affected by this condition are relieved of their symptoms by specific therapy, particularly when the etiology has been determined, and we have found that nonspecific means, such as nasal surgery, certain drugs, and endocrine products have been most disappointing.

Surgery is indicated only when there are anatomical defects, polyps, and secondary infections of the sinuses. As a matter of fact, the latter will very often clear up if the allergic condition is controlled.

In closing may I state that the many refractory and repeated upper respiratory conditions will disappear if treated on an allergic basis, and many complicating conditions such as sinus disease, bronchial asthma, and its sequelae might be obviated, making for a healthier, happier and better child.

CHAIRMAN RATNER.—Dr. Piness, I do not think that there can be much discussion of your paper because you have covered the field so well and we all agree with practically everything you said.

There are just two points which you brought up that I must comment on. You say that minor allergy does not exist. This is surprising, for there are all degrees and kinds of reactivity, the same as there are all degrees and kinds of so-called normality. The next point which I would like to stress is that I believe that your work done in the Arizona valley with the development of hay fever in a group of individuals who never suffered from hay fever prior to entering this community is probably one of the most important contributions that I find in the literature to indicate that heredity plays a minor role in allergy, for those people without positive family histories developed hay fever before the others who had positive family histories.

DR. PINESS.—Regarding the question of minor and major allergies, I contend that any individual who has an allergy of any kind at all is suffering from a major effect, and, regardless of whether the symptoms be mild or severe, he still is potentially predisposed to having all of the severe types of allergy. I do not think we can measure allergy by degree since it is a constitutional disease.

CHAIRMAN RATNER.—It seems unnecessary to summarize this discussion at this late hour because I believe my collaborators have done such a thorough job. I want to leave you, however, with the feeling that we have made no attempt to cover the allergy problem in childhood. We merely wanted to suggest to the pediatrician that he must interest himself in this problem and include a consideration of the allergic phenomena in his everyday practice. No period from earliest infancy throughout childhood is devoid of the possibility of hypersensitive reactivity. The pediatrician, as Dr. Smyth has brought out, is in intimate relation with his patients and has the opportunity to see these phenomena from their beginnings—free from the complications so often encountered in adult life. Early recognition offers the hope of introducing prophylactic measures and I hope my colleagues will bear with me if I venture the following statement: Although there will always be the need for the highly trained allergist, the time must come when the facts gleaned from the maze of work that is now being carried on in this field will be formulated into broad principles which may be readily applied in general pediatric practice.

I trust that you have all derived as much profit from this discussion as my colleagues and I have in preparing for it. It was a pleasure to present some of our viewpoints to you.

Meeting adjourned at 10:45 P.M.

EIGHTH ANNUAL MEETING OF THE AMERICAN ACADEMY OF PEDIATRICS

DEL MONTE, CALIF., JUNE 10 AND 11, 1938

Round Table Discussion of Sulfanilamide

Chairman, Dr. Paul M. Hamilton, Alhambra, Calif.

CHAIRMAN HAMILTON.—During its three and a half years in the limelight of American medicine, sulfanilamide has inspired more clinical and laboratory investigation than any other development of its generation. Medical and even lay literature has reached stupendous proportions as workers have attempted to evaluate the merits, the dangers, and the mode of action of this remarkable new healing agent. And yet many fundamental questions remain either partly or totally unanswered.

From this vast and in many respects still debatable field only a limited area can be surveyed in the present summary. We shall concern ourselves therefore only with those phases which have a clinical application, and only with those conditions which may be seen by the pediatrician. Most of the comments will be based upon cases we ourselves have treated, though in most instances similar observations are plentiful in the literature. For a concise summary and bibliography one may refer to Holman and Duff.[1]

Mode of Action

The mode of action of sulfanilamide is not yet fully established. It seems certain that the actual destruction of bacteria is accomplished by the natural defense mechanisms of the body, aided in some way by the drug. Sulfanilamide is only weakly bactericidal in vitro, and, contrary to experience with true germicides, its efficiency is enhanced when various body fluids are added to the media. When added to specific antibody, the increase in potency is greater than would be expected from a simple additive effect. Long and Bliss[2] believe that the action is one of bacteriostasis and that the leucocytes are an indispensable part of the process, even though it is not one of simple phagocytosis. Osgood[3] believes that the drug in some way neutralizes bacterial toxins, thus permitting free attack on the organisms by all the mechanisms of body defense. Response is regularly greater and more rapid during the stages of active tissue change than in the more chronic phases of infection, such as the formation of walled-off abscesses. Rather contradictory observations are made that while clinically recovered animals may harbor the infecting organism for a long time, other animals may die with sterile organs. At present we may only say that the drug is not in itself strongly bactericidal.

Toxic Effects and Complications

The mechanism behind its toxic effects and complications is likewise incompletely understood. These actions of the drug are so numerous and varied that they must be considered separately. Despite their imposing array, the drug is relatively innocuous provided it is properly used and the patient carefully watched for evidence of serious reactions.

Cyanosis occurs with such frequency as to make it appear almost a concomitant of intensive treatment. It has most often been ascribed to methemoglobinemia; sulphemoglobinemia has also been demonstrated repeatedly, sometimes when no other sulfur medication has been given; and in some instances it occurs without

either of these conditions. To explain this, Marshall and Walzl[4] postulate a black oxidation product which stains the red cells without measurably affecting their functioning ability. Hartmann[5] feels that the cyanosis is nearly always due to methemoglobinemia, and cites good results in treatment and prevention by the use of methylene blue either by vein or by mouth. Thus it appears that the cause of cyanosis is not always the same, and that at least in some instances it is not clearly understood.

Only rarely does cyanosis embarrass respiration or otherwise distress the patient, so that its appearance need not necessarily interfere with treatment. When due to methemoglobin, it can be relieved by methylene blue or oxygen, and it tends to disappear rapidly with discontinuance of the drug. Sulphemoglobinemia tends to be more severe and may persist for days after the sulfanilamide is discontinued.

Acidosis has been anticipated as a frequent result of intensive treatment and has been demonstrated through reduced carbon dioxide combining power. Hartmann,[5] however, has recently presented evidence to show that alkalosis is the primary response, and that such degree of acidosis as may occur later is no more than an exaggerated compensatory reaction. It has also been observed that nonfebrile patients, such as those with gonorrheal infection, usually have an alkaline urine. This naturally raises the question whether acidosis (when observed) is perhaps due to the disease rather than the drug. Proceeding on the assumption that acidosis is liable to occur, it has been our custom to give ⅙ molar sodium lactate solution, 10 c.c. to each 100 c.c. of 1 per cent solution of sulfanilamide, when given subcutaneously, or sodium bicarbonate in equal amounts when given by mouth; with the added precaution of frequent urine tests to be sure that the pH does not fall below 5. Hartmann stresses the need for maintaining chlorides and suggests a mixture of sodium lactate and Ringer's solution as being superior to sodium bicarbonate.

Anemia of great severity may occur, though fortunately it is not common. It is of the hemolytic type and may occur with such rapidity following the first dose as to suggest sensitivity, or it may come later (three to seven days) as if due to a cumulative action of the drug. Keefer[6] states that the outcome in these cases is good if the drug is stopped and transfusions are given, but our own experience has not always been so fortunate. We have seen hemoglobin drop from 80 per cent to 40 per cent in two days, despite transfusions, and continue to drop until death occurred. The only safeguard against this type of reaction is repeated blood examinations, with cessation of treatment and immediate transfusion at the first evidence of anemia. In this connection it should be remembered that a slight drop of 5 per cent to 10 per cent in hemoglobin is common during the first day or two and need cause no alarm unless it continues or accelerates.

Agranulocytosis is rare, but it is of serious import when it occurs. It tends to occur when considerable amounts of sulfanilamide have been given, and like the anemia should be anticipated by frequent blood examinations. It is treated with pentnucleotide K19 and transfusions, but it is difficult to control and may cause a fatal outcome.

Skin reactions which tend to take the form of a morbilliform rash are not uncommon. Other types of rashes may also occur, sometimes to the extent of an exfoliative dermatitis. Photosensitivity is a possibility which calls for protection of the patient from unnecessary exposure to sunlight.

Fever appearing for a few days after the disappearance of all evidence of the disease may be due to the drug. This fever is usually not high and has little effect on the patient, but it may be confusing from a therapeutic standpoint.

Malaise is common, and especially in ambulatory patients it may be so severe as to lead them to refuse treatment. It is seldom extreme in bed patients.

Psychoses are reported, but are very rare unless one should include mild confusion, depression, and moroseness, which are common. Both excitement and semi-stupor have been seen.

Jaundice is a warning of possible liver damage, or of hemolytic anemia. It tends to disappear if dosage is stopped.

Nausea is rather frequent, especially when the drug is given by mouth; *diarrhea* occurs occasionally; *toxic neuritis* and *deafness* for a short period have been reported.

Indications

Indications for the use of sulfanilamide are in some respects still ill defined, though its chief uses are fairly well established. It was first used against the staphylococcus and brilliant results have been obtained with this organism, but, in general, results have been erratic and disappointing. Possibly its greatest application has been with the streptococci of the Lancefield group A, which includes most of the streptococci ordinarily pathogenic to man. The beta (or hemolytic) organism is especially susceptible; some strains of the anhemolytic variety almost equally so; while *Streptococcus viridans* is resistant. Both meningococcic and gonococcic infections are treated with great success, gonorrheal ophthalmia in particular showing dramatic improvement over previous methods. The usual organisms of urinary tract infection respond well, with the exception of *Streptococcus fecalis*. The pneumococcus is sometimes though not always susceptible, and there is some reason to believe that a combination with type-specific serum may prove superior to either alone. Undulant fever has been treated with apparently good results, and also malaria; and experimentally, at least, it seems effective in choriolymphocytic meningitis.[7]

Clinically it is of no value in typhoid fever, although in mice it does have a definite protective effect; poliomyelitis does not respond,[8] and neither does non-specific laryngitis, although it is commonly considered a streptococcal infection (incidentally, we have had great difficulty in recovering the streptococcus from our cases).

Contraindications

Contraindications are relative only and may alter the method of treatment rather than preclude it entirely. Gross *kidney damage* is not likely to be aggravated, but blood concentration of sulfanilamide should be watched because of diminished excretion. Marked *anemia* indicates special vigilance in watching for possible hemolysis; and a *low leucocyte count* is similarly significant. In the presence of either of these, other treatment is preferable if available. *Sulfur* in any form taken concurrently predisposes to sulphemoglobinemia. *Jaundice* may sometimes have dangerous significance.

Precautions have already been indicated. They consist above all else in repeated and careful blood examinations. Urine examinations especially for acidity should not be omitted, and we have learned that a smoky appearance of urine often precedes a severe reaction. The possibility of idiosyncrasy to the drug should be borne in mind; and variations in blood concentration with identical doses in different individuals may make blood titration desirable at times.

Dosage

Dosage is tending toward standardization at 15 grains for each 20 pounds of body weight per day, sometimes with the entire first day's amount given at the first dose when the subcutaneous route is employed. It is usually stated that, provided vomiting does not occur, the oral route provides essentially the same speed and completeness of absorption as does the subcutaneous method. We have insufficient data to offer, but we have felt that the subcutaneous route is more uniform and

certain and have found no reasons to avoid it. The solution for this purpose is made up with normal saline, and can be made in 1 per cent strength by heating. The sulfanilamide will then stay in solution at ordinary room temperature, if it has been stored in the refrigerator it can be redissolved by heating. We have found no deterioration in solutions stored as long as two months. When necessary, it may be sterilized in the autoclave at about one-half the usual pressure. Antacids have already been discussed.

Several factors indicate that the question of dosage should not be considered as arbitrarily settled in every instance. It is anticipated that the dosage indicated will produce a blood concentration of about 10 mg. per cent within about four hours, with only a slightly lower concentration in the spinal fluid. This concentration is assumed to be optimal for most cases, but we have found that some patients recover rapidly with a considerably lower concentration; in like manner, it seems possible that some failures might be avoided if a higher level were maintained, which apparently can often be done without serious effects. Thus it may be that further study may show that some diseases may be treated with much less intensity than others. Again, the recommended dosage may produce a blood concentration far below that expected of it, in our experience sometimes falling as low as 3 or 4 mg. per cent, presumably because of unusually rapid excretion. In such instances, in the absence of evidence of undue toxicity, the dose may be increased far beyond the usual amount until the desired concentration is finally reached. In one instance of a young adult with epidemic meningitis we finally gave 1,100 c.c. of 1 per cent solution in one day, with immediate sterilization of a hitherto intractable spinal fluid and complete recovery. With present methods of rapid blood titration we may expect light on some of these questions in the near future.

Sulfanilamide is excreted rather rapidly by the kidney through glomerular filtration, and appears in the urine partly unchanged and partly conjugated in the acetylated form. The blood concentration is insignificant twelve hours after it has reached its maximum.

Results

With these generalities in mind, it is desirable to consider individually the more important diseases in which sulfanilamide is indicated, and to attempt to estimate its value. Many factors inherent in the shortness of the period in which it has been used preclude exact conclusions, but when results differ markedly from those hitherto obtainable the underlying trend at least is indisputable. When figures are given, these limitations must be realized until further experience permits greater accuracy.

Erysipelas has been notably amenable to treatment. It may confidently be expected to respond definitely in the first twenty-four hours, and very commonly the skin is almost clear, and the temperature is normal during the second day. Treatment should be continued for several additional days or relapse is liable to occur.

Of our 105 treated cases, 73 were discharged from the hospital within seven days; 30 of the remaining 32 were discharged during the second week; and 2 died. These two deaths deserve special comment, as they illustrate some of the dangers of sulfanilamide.

The first was a man, aged 54 years, admitted with facial erysipelas of three days' duration, and classed as moderately severe. He was given sulfanilamide by mouth, and by the third day the disease had subsided; but on that day jaundice developed, the patient became confused, and hemoglobinuria appeared. His hemoglobin dropped from 88 to 71 per cent the first day, and continued to fall despite daily transfusions of 500 c.c. each until death occurred three days later. The white count was 28,000,

with over 90 per cent granulocytes. Fragility tests showed hemolysis beginning at 0.5 and complete at 0.32, the control being 0.44 and 0.36. The blood serum was coffee colored; hemoglobinuria was constant; cyanosis began the second day. The total dosage of sulfanilamide was 255 grains over a period of four days, and the blood concentration the day symptoms began was 3.3 mg. This death is ascribed to acute hemolytic anemia due to sulfanilamide.

The second death was an infant of 22 days, admitted after one day's illness, with erysipelas over the abdomen and a temperature of 105° F. The child was slightly jaundiced, but because of his critical condition sulfanilamide was begun at once, the dose being 35 c.c., 40 c.c., and 20 c.c. of 1 per cent solution daily for the first three days. During this time the rash faded very rapidly, and on the third day the temperature was 98° F. The temperature rose to 102.6° F. on the fifth day without apparent reason other than a mild diarrhea. The hemoglobin was found to be 60 per cent as compared with 87 per cent the day of admission; the white cells numbered 32,650, of which 59 per cent were polymorphonuclears. From 10 to 15 c.c. of sulfanilamide solution had been given daily, but the blood showed only a trace of the drug. A transfusion was given and the sulfanilamide stopped, but it had to be started again on the eighth day because the erysipelas recurred. By the following day the jaundice had markedly increased; the icteric index was 40 units; the van den Bergh, prompt direct. The drug was again stopped and daily transfusions given, but the child died on the eleventh hospital day with acute hemolytic anemia, liver damage, and erysipelas. The total dose of sulfanilamide was 170 c.c.

Scarlet fever should a priori be most favorably influenced by sulfanilamide, but for some reason this logical expectation is not fulfilled. For some time we have given it to attempt a comparison of efficiency with convalescent pooled human serum, both as to the disease itself and also its complications. So far as immediate abatement of signs and symptoms of the disease is concerned, this comparison has given all the advantage to the serum. With the latter, both rash and fever were found to disappear almost miraculously in the first twenty-four to thirty-six hours, whereas under sulfanilamide treatment these persisted for some days and the patients seemed to have a dull malaise possibly even more marked than in the untreated cases. In the treatment of complications, however, sulfanilamide seemed to give quicker and more certain relief than did the serum.

The efficiency of serum in preventing complications has been so gratifying that for some time we made no attempt to evaluate sulfanilamide in this respect. Over the five-year period before we began to use serum, our complication rate had been between 35 per cent and 40 per cent, whereas with serum in 109 cases treated up to last October, there had been only 9 complications. When we began to compile the records of the sulfanilamide-treated patients we found that they too showed a decreased complication rate as compared with the previous figures, and as more cases have been treated we now find, somewhat to our surprise, that the sulfanilamide group shows a slightly better percentage than does the serum group.

Among 194 previously uncomplicated cases receiving serum, 25, or 13.4 per cent, developed complications; while among 113 such cases treated with sulfanilamide there were 13 complications, or 11.5 per cent. It should, of course, be emphasized that these figures are inconclusive, both because of the small number of cases and because of the lack of concurrent control cases; but even so, the disparity between cases treated by either method and those of past years with no specific treatment at all is at least suggestive.

Dosage in these groups was: sulfanilamide, full dose two days, ⅔ dose three days, ⅓ dose five days; serum, 40 to 60 c.c. intravenously on admission.

The complications in each group are listed below:

Complication	*Serum*	*Sulfanilamide*
Cervical adenitis	11	8
Peritonsillar abscess	1	1
Otitis media	4	2
Recurrent scarlet	0	2
Paronychia	4	0
Pyrexia undetermined	2	0
Nephritis	2	0
Chalazion	1	0
Cellulitis	1	0

Gonorrhea in its common forms of urethritis and vaginitis has been treated extensively with sulfanilamide. First reports were more enthusiastic than later ones, due to the discovery that some patients apparently cured showed relapses. There is rather frequently some difficulty in establishing criteria of cure, in that organisms may be found under the microscope which will not grow on culture. The acute case in the male may be expected to show about 75 per cent success within two weeks; if cure is not established within this time, other methods are likely to be needed. Female patients seem to respond less well, although many reports testify to the definite value of the drug; and evaluation is made more difficult by greater uncertainty in demonstrating cure. Chronic cases in both sexes show much poorer results.

A blood concentration of at least 10 mg. per cent must be maintained in these patients for good results, and medication should continue for two weeks after smear and culture are negative. Antacids are rarely necessary. Malaise under treatment may be so worked as to make the patient refuse to continue unless he can go to bed.

Gonorrheal ophthalmia responds to sulfanilamide phenomenally well, and, since to my knowledge no series so extensive as our own has been reported, it seems worth while to recount our experience in some detail.

Before the advent of sulfanilamide, using almost constant eye irrigations plus many combinations of local disinfectants of the silver group plus occasional nonspecific or "shock" therapy plus attempts at specific therapy in the form of gonococcus antigen and the like, it took us an average of almost three weeks to obtain our first negative eye smear and culture, and almost a month to discharge the patient. In addition, especially among adult patients, there was a most distressing toll of lost or impaired vision. Since beginning to use sulfanilamide, we have treated 21 cases with 18 cures and 3 failures; the first negative eye smear and culture has usually been obtained in less than forty-eight hours; and no eye has suffered any impairment if it was undamaged when treatment was begun.

Treatment at first consisted of the previous routine plus sulfanilamide in regular doses. Later local drug treatment was less rigorously performed, and in the last few cases has been omitted entirely without loss of efficiency; whether it can be permanently discarded is not yet certain. Irrigations were carried out with great care in every case as long as discharge appeared, regardless of whether the smear and culture had become negative, and often enough to keep the eye clean even though this might require almost constant irrigation. This seems an indispensable part of the program, as the pressure of exudate when allowed to accumulate tends to cause corneal ulceration even when infection is subsiding. If ulceration was already present, treatment was given with 1 per cent of silver nitrate in the usual way.

The patients successfully treated included 10 adults, 2 children aged 5 and 9 years, and 6 infants under 30 days of age. The failures were all in infants, two of them premature; these deserve special comment as they illustrate points in treatment which I believe are important.

The first was a 4 pound premature infant admitted the eleventh day of the disease. Under treatment, smear and culture became negative within thirty-six hours, and the baby was sent home after smear and culture had remained negative for five consecutive days. Five days therafter it was readmitted, and this time the organisms disappeared with two and one-half days of treatment. This patient may have relapsed because treatment was stopped too soon, or it may have been reinfected by its mother who was known to have gonorrhea.

The second case was also a premature infant weighing 4 pounds 2 ounces admitted after one day of illness. This child had negative eye smears and cultures after twenty-four hours and for the five succeeding days, when the drug was stopped because of vomiting. The same day there was a relapse in one eye and although sulfanilamide was resumed at once it appeared to have no effect whatever. The baby finally recovered, but only after seventy-seven days in the hospital under all the treatment of the old methods plus repeated attempts to get results with sulfanilamide. This case illustrates the possibility that organisms may become resistant to this drug if they are not promptly and completely eliminated by it and suggests that possibly treatment should not be stopped until at least a week after the organisms disappear.

The third case, a 6 pound 4 ounce baby admitted after seven days of illness, illustrates somewhat the same points. This child showed an immediate and marked decrease in discharge from the eyes, and the dose of sulfanilamide was decreased despite the fact that smears were still positive. The eyes became worse immediately. Dosage was increased at once, but cure was very slow; the child was in the hospital forty-seven days. Obviously treatment had been inadequate.

These cases are too few for statistical significance, but no one seeing them could question the dramatic effect of treatment, and as the discussion of the failures shows, one might possibly get even better results as the series progresses.

Meningitis is one of the more serious conditions in which sulfanilamide has been used with particularly good effect. Our own experience with the meningococcic variety has been limited to 20 cases treated with sulfanilamide alone, in addition to which there have been 25 others treated with this drug plus one or more other methods. These do not lend themselves well to a comparative analysis to determine the relative worth of the various mediums used, inasmuch as the number of patients is small and those who received more than one type of treatment may well have had more severe infections. However, out of 109 patients receiving sulfanilamide, antiserum, antitoxin, or combinations of these agents, the group treated with sulfanilamide alone showed a mortality of 10 per cent, which is much lower than that of any other method or combination of methods. A great deal more work will be needed to establish exactly the relative merit of these various preparations, as both therapeutic efficiency and therapeutic hazard must be determined; and it seems unlikely that any one of them will be able to supplant the others entirely. At present it would seem wiser to consider sulfanilamide as simply an extremely valuable aid in this serious disease and to attempt no accurate comparative evaluation.

We have had one patient with pneumococcus Type 32 meningitis, who recovered following drainage of a sinus plus sulfanilamide therapy. Several cases due to the streptococcus appear in the literature; we have had two, with one recovery. The drug has been ineffective against the influenza bacillus.

Pyelitis and allied urinary tract infections, when due to any of the common organisms except *Streptococcus fecalis*, have been shown to respond to sulfanilamide at least as well as to any of the other methods commonly used. As the drug is excreted

through the glomerulus and partially reabsorbed through the tubule, it should be able to attack kidney infections from both the blood and urinary streams. Its effect is usually greater in alkaline urine and has been shown experimentally to be greater when urine is added to the ordinary culture media. Helmholz[9] in particular has studied this type of infection.

Undulant fever, which so far has resisted all efforts toward specific therapy, may prove at least to some extent to be amenable to treatment with sulfanilamide. We have had four cases in which the temperature has become normal within a week and has remained so, and I have learned of three similar cases within the past few months. This disease is so uncommon that final evidence may be slow in coming, but it would seem that an attempt at treatment with this drug is justified.

Minor conditions in which sulfanilamide may be indicated include simple *cervical adenitis,* in which it is strikingly effective in most instances; *otitis media,* which usually responds unless due to a resistant organism but which must be treated as long as there is any discharge if relapse is to be prevented; *mastoid infections,* in which it would appear that surgery is sometimes avoided; *streptococcal infections of the throat;* and countless others. At present it is considered wise not to treat mild infections which may be expected to resolve satisfactorily under other treatments because of the slight but definite hazard of the drug itself; and in no event should intensive therapy be attempted unless the patient can be properly watched and necessary laboratory data obtained.

This summary of a remarkable new drug is admittedly incomplete; even our total knowledge of it is incomplete. Enough is known, however, to establish its undoubted potency and wide application. There is reason to believe that it may usher in a series of advances in chemotherapy as the possibilities of other related compounds are discovered.

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DR. E. S. PLATOU (MINNEAPOLIS, MINN.).—We have attempted to compare a series of one hundred scarlet fever patients treated with sulfanilamide during 1937-1938 with an equal number of controls who did not receive the drug. The two series, although not comprised of alternate cases, ran concurrently and were comparable with respect to age, severity, and duration of disease prior to treatment. Although the criteria for evaluating our results may be subject to criticism, some observations have been made which we believe are significant and seem to suggest that sulfanilamide is of value in the treatment of scarlet fever.

The drug was administered orally except to patients with nausea or extreme toxemia. The latter were given an initial large dose subcutaneously in the form of 1 per cent solution in normal saline. The dosage used was that recommended by Long and Bliss for severe infections; an initial massive dose of 0.05 gram per pound of body weight and a maintenance dose of 0.03 gm. per pound per twenty-four hours. It is our impression that per unit of weight, children tolerate the drug better than adults. With the exception of the development of leucopenia in two cases, a fever and rash in two additional cases, in which we were compelled to

discontinue therapy, no serious complications were encountered with the drug. Cyanosis without sulphemoglobinemia was observed in several instances but therapy was continued without any ill effects. The dosage was gradually decreased but was continued on an average of twelve days. Too early discontinuance of the drug was believed to be the cause of the appearance of mild complications in a few of our cases. The best results were obtained when sulfanilamide was continued during the entire convalescent period. The fever curve in the treated cases, once it became normal, remained so in practically all cases without complications, whereas the untreated cases showed irregular rises in temperature, often without demonstrable explanation for this rise.

In our treated cases the rate of recovery from the acute toxemic phase of the disease (6 days) was no more rapid than it was in the control cases (6 days). The sulfanilamide-treated cases did not show the prompt subsidence of toxic symptoms such as we have observed following the administration of serum. The incidence of complications was 41 per cent in the controls as compared to 8 per cent in the treated cases. There were nine suppurative conditions in the control cases as compared to one in the treated series. In a few septic cases recently treated by massive intravenous doses of serum combined with sulfanilamide, the results have been so striking as to suggest a synergistic effect.

DISCUSSION

CHAIRMAN HAMILTON.—Dr. Platou's figures are most impressive. It would be of interest to see what can be done with both treatments.

DR. PLATOU.—We had six cases by the combined treatment. The results were dramatic and the complications nil.

DR. S. H. NICHOLS (Asbury Park, N. J.).—What are your results in the treatment of throat conditions, for example, acute tonsillitis?

CHAIRMAN HAMILTON.—We have had some good results and some poor results. I have no controlled group to report and would use it only if the patient were very sick.

DR. NICHOLS.—I have used it in 25 cases with very poor results. In a few cases it seemed to help.

DR. R. P. SEITZ (San Francisco).—Have you used sulfanilamide in pneumonia?

CHAIRMAN HAMILTON.—In pneumonia our results are discouraging. We have had better results with serum and are now attempting serum and sulfanilamide for additive effects. We have not used serum very often in children.

DR. FAIRFAX HALL (New Rochelle, N. Y.).—Sulfanilamide in rheumatic fever shows bad results.

CHAIRMAN HAMILTON.—It is useless.

DR. V. E. TAPPAN (Tucson, Ariz.).—Reports from the Rockefeller Institute show fair results.

DR. G. L. KAUFMAN (Chicago).—What results were obtained in combined treatment in meningococcic meningitis?

DR. PLATOU.—We used it concurrently in 22 cases with no deaths.

DR. G. J. LEVY (Memphis, Tenn.).—Can sulfanilamide be used intraspinally?

CHAIRMAN HAMILTON.—It can be done, and there are no contraindications. The spinal fluid concentration is only slightly less than the blood concentration when sulfanilamide is given by mouth. The only advantage of giving the drug

intraspinally is the speed of administration, in that when given, it is there at once. Spinal punctures in meningitis are only for relief of pressure, cell counts, and criteria of prognosis.

DR. SEITZ.—What results have you had in influenzal meningitis? I know one patient it apparently cured.

CHAIRMAN HAMILTON.—We have had two patients die, and sulfanilamide failed to affect them in any way.

DR. R. G. SHARP (SAN DIEGO, CALIF.).—We had one patient in the San Diego Hospital who seemed to have been cured by sulfanilamide.

DR. E. J. LAMB (SANTA BARBARA, CALIF.).—We have treated four cases of spider bites (black widow?) with sulfanilamide. A one-month-old infant died after twenty-four hours and one four-year-old child died within twenty-six hours after being bitten. The patients who recovered showed immediate results.

DR. TAPPAN.—Sulfanilamide gives results in chronic brucella infections.

CHAIRMAN HAMILTON.—How definitely chronic?

DR. TAPPAN.—In four cases of unexplained fever of three to four months' duration.

DR. HALL.—In mastoid infections sulfanilamide may bring fever to normal, but there are still some streptococci present in the mastoid cells, and the treatment should be continued over a long period of time.

DR. TAPPAN.—It is very important to continue treatment even after improvement as some bacteria are left which are still active.

DR. HALL.—Is six weeks too long to continue treatment?

CHAIRMAN HAMILTON.—Not necessarily. Two weeks are necessary in gonorrhea cases beyond the time of a negative smear.

DR. TAPPAN.—The results in tuberculosis have been undesirable.

CHAIRMAN HAMILTON.—The results in laboratory animals are poor.

DR. TAPPAN.—It has rendered animals less susceptible.

DR. E. C. MITCHELL (MEMPHIS, TENN.).—Sulfanilamide is of no benefit in malaria. We have treated 75 cases of pyelitis in the last two years. Sulfanilamide will clear up streptococcal infections, usually clears colon infections, but in staphylococcal infections the results are not as good. In gonorrheal vaginitis it will clear up the discharge, but it often returns.

DR. S. C. HENN (CHICAGO).—This seems to be a common occurrence. We often find the bacteria under the microscope but the bacteria will not grow. We always try to check the patient by culture as well as smear.

DR. G. W. KUTSCHER, JR. (ASHEVILLE, N. C.).—The pneumococcus acts the same as the gonococcus on culture.

DR. H. F. DIETRICH (LOS ANGELES, CALIF.).—I would like to report two cases.

CASE 1.—A child whose appendix had ruptured six days before was treated by surgical drainage; large doses of sulfanilamide were started and thirty hours after admission there was noted a dramatic improvement.

CASE 2.—A seven-year-old girl was ill for four or five days with general peritonitis; culture of the abdominal fluid revealed pneumococcus and beta streptococcus. Large doses of sulfanilamide were started and within twenty-four hours the patient had a critical drop in her fever. She went home in two weeks.

QUESTION.—Can sulfanilamide be used to begin the treatment of pyelitis?

CHAIRMAN HAMILTON.—Sulfanilamide is rapidly superseding previous medications in pyelitis. Pediatricians rarely isolate the organism in private practice.

DR. DIETRICH.—The routine use of sulfanilamide in pyelitis should be discouraged; 80-90 per cent of the infections are self-limited, and we are inviting undue risk by using sulfanilamide routinely. If we segregate those with chronic or obstructive cases, sulfanilamide is indicated.

DR. NICHOLS.—When is pyelitis self-limited? What are the criteria?

DR. DIETRICH.—The great majority of cases become sterilized in eight days; the rest in five to six weeks. If it persists four weeks, then the infection is certainly refractile and suggests the use of sulfanilamide.

DR. HENN.—Twelve years ago one of my patients (a boy) had 600 white blood cells per cubic centimeter. He was operated on for diverticulum of the bladder, and he continued to have pus in the urine. After ten years one kidney was removed, and he still had pus. He was treated with all the antiseptics with no result. Eight months ago he was given sulfanilamide in "tonic" doses (5 gr. every 4 hours), and the urine was clear in one week. The pus recurred in ten days and sulfanilamide therapy was repeated for ten days. Since then the urine has been absolutely clear.

DR. SEITZ.—What about "tonic" doses?

CHAIRMAN HAMILTON.—I see no reason for "tonic" doses. If using sulfanilamide one should give enough to get a concentration of 10 mg. per cent.

DR. MITCHELL.—I believe the use of alkalies hinders the effectiveness of sulfanilamide and have observed no benefit from them. For malaise, cyanosis, and other distressing symptoms, I inject 10 per cent methylene blue solution (dosage 10 c.c. per 150 pounds of weight) intravenously, and it also clears up the patient's subjective symptoms.

CHAIRMAN HAMILTON.—We use methylene blue occasionally.

DR. S. G. HENRICKE (PORTLAND, ORE).—I find that in hemolytic streptococcal infections one-tenth the dosage is equally effective. In pneumococcus Type 3, full dosage, with the serum, gives good results.

DR. HALL.—Does toxicosis depend upon dosage?

CHAIRMAN HAMILTON.—Not always. It may be an idiosynerasy. There are many reports of sulfanilamide causing anaphylactoid reactions.

DR. HALL.—Small doses may cause an hemolytic anemia with rash in twenty-four hours.

CHAIRMAN HAMILTON.—If a rash appears, one should stop treatment.

DR. MITCHELL.—At the university we give 3 grains per kilogram of body weight per twenty-four hours and find sometimes this is entirely inadequate.

CHAIRMAN HAMILTON.—Do you divide your doses?

DR. MITCHELL.—Yes, we divide the twenty-four-hour dose into six parts and give it every four hours.

DR. HENRICKE.—When is the ideal time to take pooled scarlet fever serum?

CHAIRMAN HAMILTON.—Twenty-one days up to three or four months.

DR. W. W. QUILLIAN (CORAL GABLES, FLA.).—I have seen two patients treated with sulfanilamide who developed unusual blood pictures; i.e., a marked leucocytosis (34,000 white blood cells) instead of leucopenia. There were many abnormal types including 28 per cent eosinophiles. Later the blood picture gradually returned to normal. The patients' color became cyanotic though the blood concentration was only 9 mg. per cent.

DR. LEVY.—We try to maintain a concentration of 20 mg. per cent unless unusual toxic symptoms appear; we also control our patients with daily blood counts. We give an initial dose of 150 grains and rarely use subcutaneous administration because we think the oral administration ideal. In newborn infants we use the nasal tube. We have had one failure in gonorrheal conjunctivitis. This was a 29-year-old negro who had an initial 150 grain dose then 30 gr. every four hours. He received 450 grains before a toxic condition of jaundice and anemia occurred. We gave him glucose intravenously and a blood transfusion of 600 c.c. The anemia and jaundice progressed, and he developed anuria in eight hours. There was no autopsy, but our diagnosis was acute hemolytic anemia from sulfanilamide.

CHAIRMAN HAMILTON.—The only psychic symptoms we have noticed are dullness and confusion.

DR. PLATOU.—We have treated 16 cases of serious nephritis and had the impression that sulfanilamide did some good. The local treatment of sulfanilamide injected into a body cavity (as the pleural cavity) had no results. In my experience with the pneumococcus Type 3 it was not effective. I believe the greatest need is a test for predetermination of allergy or idiosyncrasy.

CHAIRMAN HAMILTON.—The local use of this drug has not been shown to be effective. An ointment has been used locally but not much is known about it.

DR. TAPPAN.—In what type of nephritis and in what stage was sulfanilamide used?

DR. PLATOU.—Acute glomerular nephritis, and its use is purely experimental.

DR. TAPPAN.—Aspirin given at the same time with sulfanilamide will cause toxicity.

DR. M. SWIGART (MONTEREY, CALIF.).—How much is secreted in the breast milk?

CHAIRMAN HAMILTON.—I have no definite report, but I believe the same concentration is present as in the blood and that it may have a toxic effect on the baby.

DR. HALL.—How about magnesium sulfate?

CHAIRMAN HAMILTON.—I have had no personal experience, but it should not be used.

DR. TAPPAN.—We have seen patients whose skin is very sensitive to the sun after treatment with sulfanilamide.

DR. M. M. NICHOLSON (WASHINGTON, D. C.).—Does the vitamin and mineral content of the child as he becomes ill influence the prognosis when using sulfanilamide?

CHAIRMAN HAMILTON.—I do not know of any data on this subject.

QUESTION.—If amidopyrine is a cause of agranulocytosis, how does sulfanilamide compare?

CHAIRMAN HAMILTON.—To answer this one should have a comparison of the frequency of use of amidopyrine and sulfanilamide, and one cannot do this because amidopyrine is bought so frequently over the drug counter. There are three types of infections being treated with sulfanilamide:

1. Those which sulfanilamide will cure.
2. The in-between infections, i.e., questionable cures.
3. Those infections which the drug will not affect.

We are still groping for infections sulfanilamide will cure.

DR. R. N. ANDREWS (MANKATO, MINN.).—In medicine the pendulum swings one way or the other too far. Several years ago I reported the use of urea in the treatment of pneumonia with good results. Now the subject has been practically dropped. There is no question that sulfanilamide has proved its usefulness. However, when patients die of the effects of sulfanilamide therapy, it should not be used indiscriminately. Why use it in tonsillitis when the infection is self-limited?

CHAIRMAN HAMILTON.—That attitude cannot be stressed too much.

A. L. GLEASON, M.D.
Oakland, Calif.
Secretary.

Academy News

Region I of the Academy will meet on Nov. 11 and 12, 1938, at Rochester, N. Y. Details of the meeting have not yet been announced. Dr. Paul W. Beaven, state chairman for New York, is in charge of the committee on arrangements. Dr. Stanley H. Nichols has been chosen chairman of Region I to succeed Dr. Schroeder, who died.

Region II of the Academy will meet on Wednesday, Nov. 16, 1938, at the Skirvin Hotel, Oklahoma City, Okla. This meeting will be held at the time of the Southern Medical Association. There will be a scientific session on Wednesday morning followed by round table discussions in the afternoon by invited guests. The business meeting of this region will be held at 4:30 P.M. At 7:00 P.M. there will be a joint banquet of the section on pediatrics of the Southern Medical Association and members, and the Academy members who wish to attend the meeting should write to Dr. Ben H. Nicholson, 301 West Twelfth Street, Oklahoma City, for reservations at the Skirvin Hotel, which is headquarters for the Academy.

Final announcements have been made of arrangements for the meeting of Region III at Detroit, Michigan on Thursday, Friday, and Saturday, Oct. 27, 28, 29, 1938. Headquarters will be at Hotel Statler.

The November issue of the JOURNAL will be a memorial to the late Williams McKim Marriott, who died Nov. 12, 1936. It will consist of contributions from his associates at Johns Hopkins, where he started his pediatric training with Howland, and from those who were associated with him at Washington University. The list of contributors is as follows: Blackfan, Clausen, Cooke, Darrow, Elliott, Hartmann, Hempelmann, Jeans, McCulloch, Park, Powers, Smyth, Tallerman, Utheim-Toverud and Veeder. Any one desiring an extra copy of the issue should notify the publisher, The C. V. Mosby Company, 3525 Pine St., St. Louis, at once, so that they may be provided for at the time of printing.

Dr. Ruth M. Mahon, of Grand Forks, N. D., died August 31 at Livingston, Mont., of encephalitis contracted while touring Yellowstone Park.

M. G. Peterman, M.D. has announced his resignation from the faculty of the Marquette University School of Medicine, effective September 1, 1938.

Dr. Arch B. Chappell, of Middletown, N. Y., died August 28.

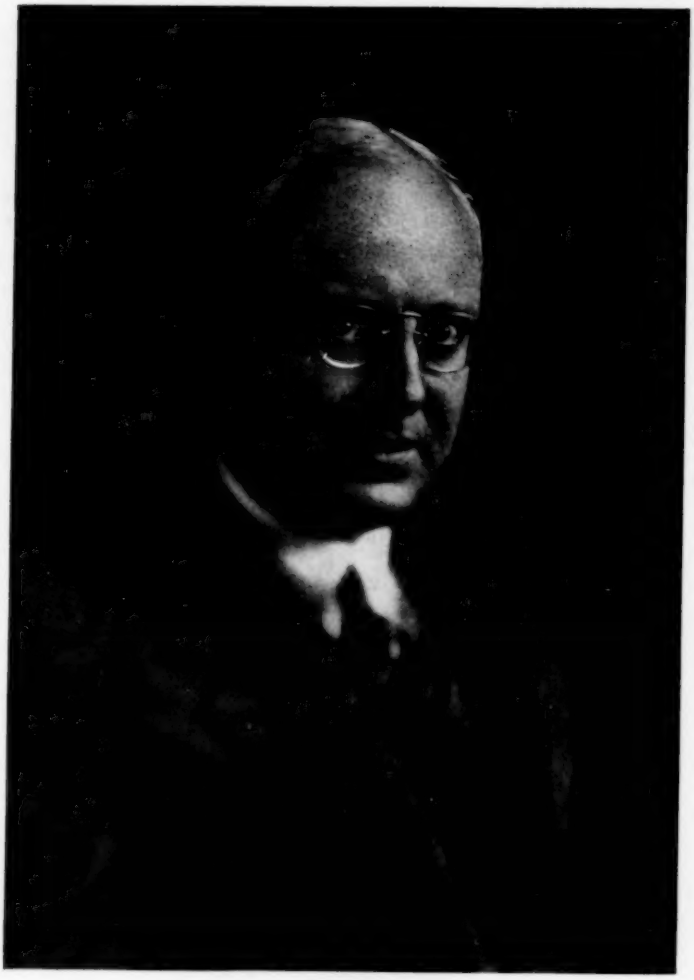
Erratum

In the account of the Eighth Annual Meeting of the American Academy of Pediatrics, which appeared in the August issue of the JOURNAL, page 263, line 31, the following quotation:

> "DR. ANDREW J. THORNTON (SAN DIEGO, CALIF.).—All the school children in San Diego have an examination every year, including a Wassermann test for $1.50."

is incorrect and should be changed to read:

> "DR. ANDREW J. THORNTON (SAN DIEGO, CALIF.).—All *food handlers* in San Diego have an examination every year, including a Wassermann test, for $1.50. A similar program for examining nursemaids and others in close contact with children might be arranged as a public health measure."



WILLIAMS MCKIM MARRIOTT
1885-1936

UNIV. OF MICH.

WILLIAMS McKIM MARRIOTT was one of the most distinguished of the group responsible for the remarkable scientific advancement of American pediatrics in the quarter century 1910 to 1935. While it is true in general that time alone, with the historical perspective, fixes the exact place of an individual in the story of any advance or movement, nevertheless Marriott's contribution was of such decided influence upon, and of such importance to, his contemporaries, that as a mark of their appreciation and respect this number of THE JOURNAL OF PEDIATRICS is dedicated to his memory. Only pediatricians, and furthermore only those closely associated with him in Baltimore and St. Louis have been invited to contribute; for if all of his friends and associates in pediatrics and other fields were included, it would be necessary to devote many issues to their contributions. Dr. Blackfan, Dr. Park, and Dr. Powers represent Marriott's Baltimore years at Johns Hopkins; Dr. Tallerman and Dr. Utheim-Toverud, those who came from foreign countries to study under him; and the remainder, his associates during the years at Washington University in St. Louis. Dr. Eliot represents the large group who served as resident physicians on his service in the St. Louis Children's Hospital.

In its relationship to pediatrics it is convenient to look upon Marriott's life and work as divided into three periods. First, his background and early training and interests which led up to, and were in large part responsible for, the brilliant second phase of active pediatric work. The third period comes when his interests centered increasingly on administrative work, and pediatric interests diminished until he reached the decision he had had in mind for several years to leave this field, a change that was made only shortly before his early and untimely death. A study of his bibliography which is appended clearly reflects these three periods.

Marriott was graduated from the University of North Carolina with the B.S. degree in 1904, when he was only 19 years old. He had majored in chemistry and during the last year of his college course was an assistant in the chemical laboratory. In the fall of 1904 he became an assistant under Wolf in the Department of Biochemistry at Cornell Medical School in New York City, where he remained for six years, teaching and at the same time studying medicine, graduating with the M.D. degree in 1910. In the fall of that year he went to St. Louis with Shaffer as an assistant in the Department of Biochemistry of the newly reorganized School of Medicine of Washington University, where he remained for four years. He had no clinical medical training or hospital experience beyond that of the undergraduate course. Correspondingly

one finds his publications during these years devoted to chemical research. It was a preparation with which few men have entered the field of clinical medicine, and naturally gave direction to the line of research and investigation which he later carried out.

It was in 1913 that I first heard him express the desire to take up problems more directly connected with clinical medicine. He had no particular interest in pediatrics and his entering the field was a matter of chance. He tried to obtain a position in a department of internal medicine, but, fortunately for pediatrics, was told they had no place for a "chemist." In 1913 an opportunity came to enter a department of pediatrics. Through unforeseen circumstances this fell through, and Howland, who was looking for a chemist in the pediatric department he was organizing in Baltimore, learning of the situation, offered him a place. As no opportunity to enter a department of internal medicine developed, he accepted and became a part of the pediatric department of Johns Hopkins in 1914. Marriott was never particularly interested in children as a problem or study, but rather in the study of disease. Once shortly before he left St. Louis, when discussing his future in San Francisco as dean and professor of research medicine, he remarked it would give him the opportunity to study some problems of adult medicine which he had in mind for many years.

He entered his pediatric years with an extraordinarily unusual technical training in chemistry, a keen, alert, analytical mind, and a scientific approach to the problems he was to undertake which foreshadowed the position he was later to hold. Furthermore he was entering at the opportune time on the special phase of pediatrics which he was to develop. Scientific progress in large part depends upon the development of methods of study, and it was just at this moment that methods of chemical research were being worked out, which to a large extent revolutionized our knowledge of metabolic processes and conditions. In this he played a prominent part. The remark of Pasteur that "chance favors the prepared mind," is eloquently exemplified in Marriott's career.

The association of Marriott and Howland from 1914 to 1917 was most fortunate and happy for both men and for pediatrics. Howland had an excellent clinical knowledge of pediatrics with an intense desire for scientific investigation, but with little technical training or knowledge of methods, while Marriott had no clinical knowledge or experience but splendid technical training. The results of their collaboration during these three years on the subjects of acidosis in alimentary intoxication and calcium metabolism in infancy are in some respects the finest work each produced. It can be said without exaggeration that with this work American pediatrics began to have a world-wide influence. Howland wished to keep Marriott in the laboratory and away from clinical medi-

cine. Marriott, however, had different ideas and insisted after the first year upon spending part of his time in clinical work. According to his associates, with his brilliant mind he developed clinical experience with an uncanny ease.

In 1917 he was invited to become head of the Department of Pediatrics at Washington University which had recently been put on a full-time basis. Despite his limited clinical training and the advice of his friends, he accepted. As it turned out, he was right in his judgment.

His clinical training with Howland and his associates had given him the best in American pediatrics at that time. His short clinical training in a way was a decided advantage, as he was uninhibited by the traditional methods of infant feeding which were taught in American schools, and with which the average young man entering pediatrics at that time had been imbued by the authority of his elders. Nor had he come under the influence of the German school whose ideas were being handed out to the many pediatric neophytes studying abroad, for previous to Howland's clinic there was no place where training in this field could be obtained in America. He thus had little to unlearn and entered pediatrics with a free untrammeled approach to the subject. Nevertheless, it required courage to attempt what Marriott did, and only an unusually brilliant and sound mind could have made a success of his new responsibilities.

It is necessary only to go over his bibliography from 1919 to 1926 to note the spread of Marriott's interest and studies during his early years in St. Louis. During this time he did important work in the further study of diarrheal conditions and parenteral infections affecting metabolism, and he turned the weight of his rapidly growing influence toward simplified methods of infant feeding which were coming into use. But to realize fully the significance of his contribution, it is necessary to take into consideration the work of his associates, as Jeans, Hartmann, and Clausen, whose work was carried on with the stimulation of his interest and counsel.

In 1923 an event took place on which many of us look back as somewhat of a tragedy. He became dean of Washington University School of Medicine. This was the beginning of a steadily progressive decreasing interest in his scientific work and pediatrics, and a steadily increasing interest and engrossment in administrative details and problems. A glance at his bibliography shows this change. It is only fair to say that Marriott liked the administrative work, but at the same time was unwilling to give up his clinical work. For years he tried to carry the full-sized load of two men on his shoulders. He worked day and night. The tragedy lies not only in the effect it had on his health, but in that, while many men had as good or even better administrative ability, one does not need the fingers of a hand to count the men with his bril-

liant scientific mind and ability. His scientific output became trivial when compared with his earlier work. It was due only to the loyal support of his two associates, Hartmann and Cooke, that he was able to carry on his hospital and departmental work during his last few years in St. Louis. It is significant of the situation that in these later years there was no such development of younger men under him as had taken place earlier. This is not a criticism of Marriott—he liked the administrative work—but simply an explanation of the change which took place in his work and productivity which is obvious to any one who studies his career. He was conscious of it himself. Once when we were returning from a pediatric society meeting in the early thirties, he replied to a remark that he had not said a word at the meeting, that he felt "out of the pediatric picture."

In 1933 he had a serious illness which left its traces. In 1935 a streptococcus infection developed which in part led him to the decision to resign at St. Louis and accept the position of dean and professor of research medicine at the University of California Medical School. He felt this would allow him to take things easier, to carry on his educational interests, while the freedom from teaching and hospital responsibility would give him the opportunity to return to the laboratory. Those of us who knew him best feel that had he lived, his years at San Francisco would have been most fruitful.

This in brief, so far as pediatrics is concerned, is the story of the meteoric career of one of the most brilliant minds that has flashed across the field of pediatrics in America. His influence through his scientific work and writings, through the hundreds of students and practitioners who sat under his clear and forceful teaching, and particularly through the development of his associates who now hold places in many medical schools will last for many years.

It is not the place in a limited biographical note of this kind to discuss McKim Marriott as an individual, the concentration of his interest in his work, his simplicity of life, his interest in medical education, and his work as dean of the School of Medicine. In pediatrics he had the respect and loyalty of the men with whom he was associated, and this in itself speaks sufficiently for his character.

—*Borden Veeder.*

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